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APPROACHES TO THE ASYMMETRIC SYNTHESIS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

A Thesis
Submitted Towards the
Degree of
Doctor of Philosophy

by

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CONTENTS

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And thanx to my family for...well...being my family.

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ALL APOLOGIES

What else should I be
All apologies
What else should I say
Everyone is gay

What else could I write
I don't have the right
What else should I be
All apologies

In the sun
In the sun I feel as one
In the sun
In the sun
I'm married
buried

I wish I was like you
Easily amused
Find my nest of salt
Everything's my fault
I'll take all the blame
Aqua sea-foam shame
Sunburn with freezer-burn
Choking on the ashes of her enemy

All in all is all we all are

Kurt Cobain

DECLARATION

To the best of my knowledge, this thesis contains no material previously submitted for a degree or diploma and contains no material previously published, except where due reference is made.

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Robert Griesbach

3 June, 1996

ABSTRACT

The aryl propanoic acid ibuprofen ((*S*)-2-[4-(2-methylpropyl)phenyl]propanoic acid) was synthesized in 96% e.e. Control of stereochemistry was achieved by use of the Sharpless epoxidation reaction, followed by reduction of the product epoxide by complex hydride with assistance by titanium tetraisopropoxide acting as a Lewis acid.

The final step was the coupling of an optically active carboxylic acid intermediate with the *iso*-butyl side chain to give (*S*)-ibuprofen. This intermediate is a bromo arene and could potentially be coupled to various side chains to give different members of the aryl propanoic acid family.

The synthesis of naproxen ((*S*)-2-(6-methoxy-2-naphthyl)propanoic acid) was also completed, in 96% e.e. Asymmetry was introduced with the Sharpless asymmetric dihydroxylation reaction followed by formation of the corresponding optically active epoxide. This epoxide was reduced by catalytic hydrogenolysis of the benzylic C-O bond to give the stereogenic centre with the correct configuration. The final step was oxidation to give naproxen.

The synthesis of ketorolac ((*S*)-5-benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acid) was attempted. A target intermediate was sought, from which the methodology established above, for the synthesis of naproxen, could be used to establish the stereogenic centre adjacent to the carboxylate group. This intermediate, from which point asymmetric chemistry would be attempted, was a diketone, which had two carbonyl groups in direct conjugation with the pyrrole ring. Many problems were experienced in the preparation of this intermediate, in attempts to attach the second carbonyl group, due to the deactivating nature of the already attached, electron withdrawing, carbonyl group. The intermediate was not obtained in workable quantities.

Another route was attempted, in which the intermediates were not stabilized by the benzoyl group, however these intermediates were too unstable to ~~work with~~ be useful. It was not realised at the start ~~of this~~ that work ~~that~~ with these pyrrole compounds would be so difficult ~~to work with~~.

INTRODUCTION

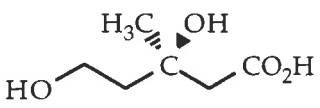
Chirality and Pharmaceutics

The importance of stereochemistry in drug action is not a new concept: there exists ample information concerning the differences in biological activities (an example is shown below), potencies, toxicities, transport mechanism and routes of metabolism of the enantiomers. Yet a rapid survey of any pharmacopoeia will confirm that most of the ~~top prescribed~~ most prescribed drugs containing an asymmetric centre are marketed as racemates.

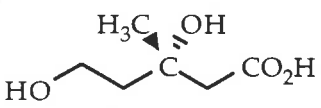
The pharmaceutical industry is presently entering a new era of zero risk, precisely targeted drug therapies. Multi-drug preparations are frowned upon and rightly so. It is easy to foresee a day when a racemic mixture will be considered as a drug with 50% impurity, as pointed out by Professor Ariens.[1]

It is, therefore, not surprising that in the past several years, there has been a tremendous impetus to develop asymmetric synthetic methods, which are of more than academic interest, as well as enzymatic and microbiological processes. Separation methods based on fractional crystallization and chromatography have also been developed.[1]

The difference in reactivity of stereoisomers in a living organism can be seen clearly, although only partially, in the following example. When a racemic mixture of mevalonic acid is fed to rats, one optical isomer is totally absorbed, and almost all the other is excreted in the urine, from which it can be recovered. The mixture has been resolved due to the difference of reactivities of the stereoisomers–the one isomer being metabolised, the other passing through the body of the rat unreacted (Figure 1).[2]



(metabolised)



(excreted)

Figure 1

Racemic drug mixtures are classified into four general groups.[3] These are

a) mixtures of an active and a relatively inert isomer,

b) mixtures of isomers with different and unique pharmacodynamic activities,

c) mixtures of isomers with opposing pharmacodynamic activities, and

d) mixtures of isomers with similar pharmacodynamic activities, although often differing potency.

The chirality issue has been given much attention in recent years by pharmaceutical companies and regulatory bodies such as the United States Food and Drug Administration (FDA). There is a definite trend towards the development of drugs as single enantiomers, with the worldwide market for enantiopure drugs rising from $27.8 billion in 1992 to $35.6 billion in 1993 and having an estimated value of up to $60 billion in 1997. One of the major factors influencing this trend is the position taken by the FDA, which was stated in May 1992 in a "Policy Statement for the Development of New Stereoisomeric Drugs". This statement addressed the chemistry, pharmacology, toxicity and clinical aspects of stereoisomeric drug molecules.[4,5] Although the FDA will continue to consider racemates as new drugs, guidelines for their approval are becoming more restrictive, with extensive testing of the individual enantiomers now required.[6]

In recent years pharmaceutical companies have been redeveloping and marketing racemic drugs, that are currently on the market, to single isomer form (so called 'racemic switches'). The commercial pressure for this is the expiration of the patent for the racemic form of the drug and the advertising potential–"twice the activity for less than twice the cost", "new, improved formula!". α-Arylpropanoic acids are one of the classes of racemic drugs that fall into this area and there is currently intense interest in finding asymmetric syntheses for these drugs.[4]

This thesis examines routes for the asymmetric synthesis of three members of the nonsteroidal anti-inflammatory class of drugs (NSAIDs): two α-arylpropanoic acid derivatives–ibuprofen (1f)* and naproxen (2f)–and a pyrrole alkanoic acid derivative–ketorolac (3f) (Figure 2).

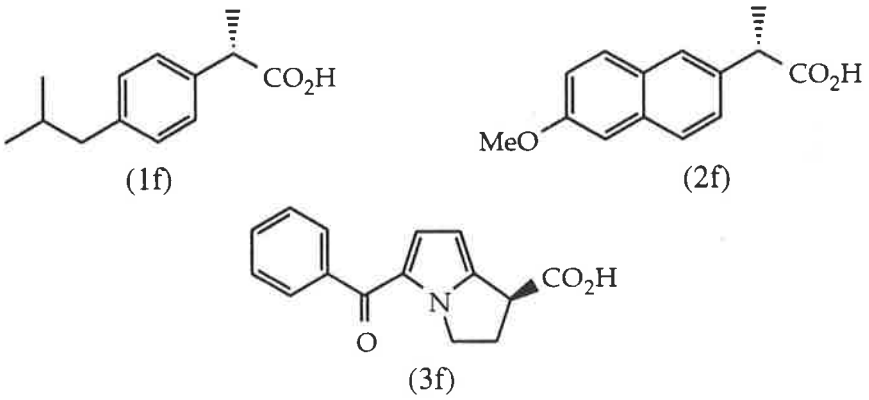


Figure 2

Ibuprofen and most of the other nonsteroidal anti-inflammatory drugs fall into the first category type (as listed on page 2) in that the non-desired isomer is relatively inert. As such the racemic mixtures of NSAIDs are not significantly problematic for the clinical pharmacologist.[3] However there is a problem in the fact that the inactive *R* isomer undergoes unidirectional chiral inversion to the active *S* isomer and the extent of this inversion varies for different patient groups.[4] Thus the actual dose of NSAID is not easily known. On examining the metabolic pathway the situation is seen to be more complex still.

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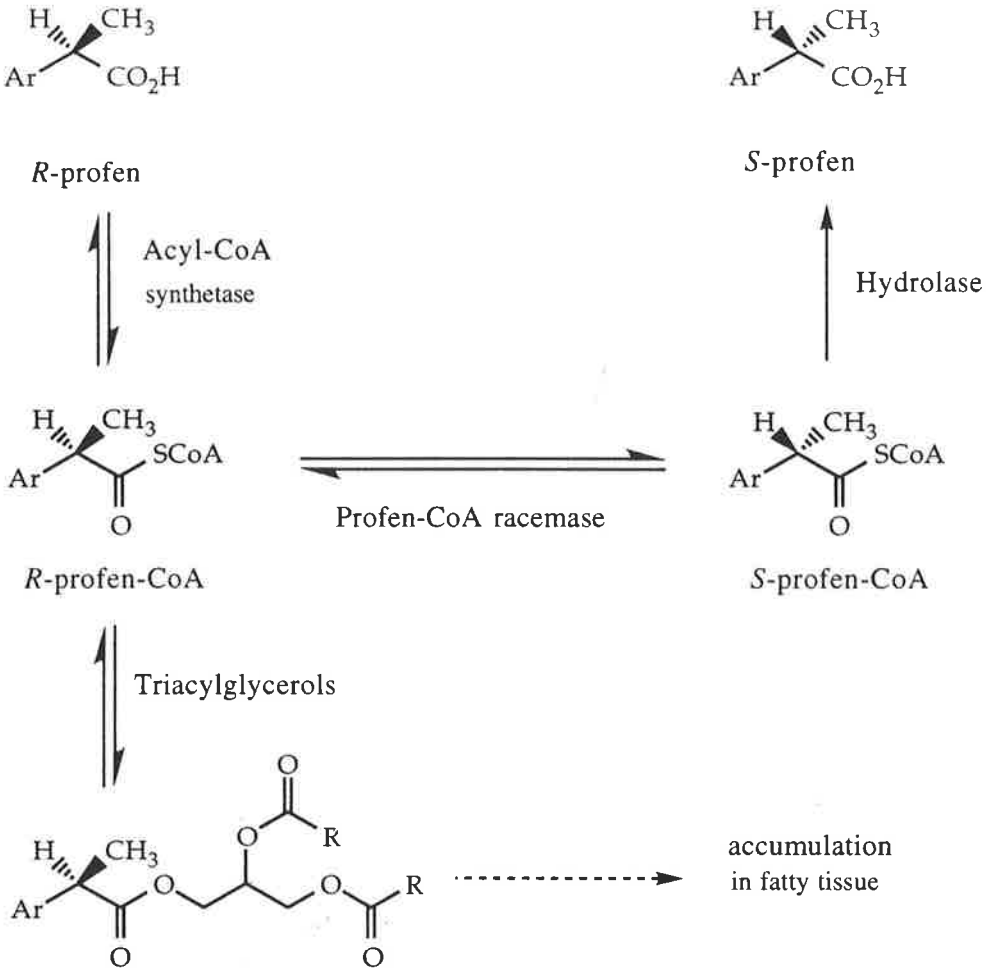
* Throughout this thesis the letter "r" after the number of a compound denotes the racemic form. Similarly, the letters "f" and "g" denote the enantiomers.



Scheme 1

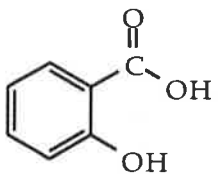
The enzyme acylcoenzyme A synthetase controls the inversion of *R* to *S*, which proceeds via the coenzyme A (CoA) thioester (Scheme 1). The racemisation of *R*-profen-CoA thioester by a racemase produces the opposite *S*-profen-CoA, which is subsequently hydrolysed to the *S*-profen. Competing with this hydrolysis is an acyl exchange mechanism with the endogenous triacylglycerols, resulting in the accumulation of *R*-profen residues in fatty tissue. Because the *S*-profen does not form the CoA thioester it cannot be incorporated into fatty tissue. Therefore there is great concern at the long term accumulation of *R*-profen residues in fatty tissue where there is unknown toxicity and the possibility of transport across the blood-brain barrier.[4]

The Inflammatory Response

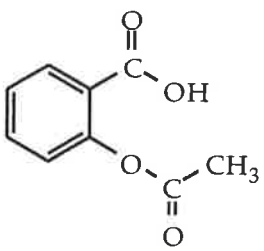
Inflammation occurs in response to injury or foreign invaders, and in this context is a protective process. It is a complex interaction of nonimmunological and immunological reactions. In some circumstances inflammation can be abnormal as when it is directed against innocuous invaders (e.g. pollens) or is directed against self (e.g. asthma, rheumatoid arthritis) which can lead to destruction of bone and cartilage and the resulting limitation of joint function. In such instances anti-inflammatory drug treatment may be necessary, and can in fact be life saving.[7,8]

History–Aspirin

Quinine from cinchona bark is one of the oldest remedies for relief of mild pain and fever. Willow bark was used in folk medicine for years for similar indications. In 1763, Reverend Edmund Stone, in a letter to the president of the Royal Society, described his success in treating fever with a powdered form of the bark of the willow. He noted that the bitterness of willow bark was reminiscent of the taste of cinchona bark, the source of quinine. The active ingredient of willow bark, salicin, which on hydrolysis yields salicylic acid (4) (Figure 3), was later found in other natural sources. Acetylsalicylic acid (5) was synthesized in 1853, but the drug was not used until 1899, when it was found to be effective in arthritis and well tolerated. Because of its greater efficacy and lower cost, aspirin rapidly replaced the natural products then in use and has remained one of the most widely employed remedies for over 90 years.[8]



(4)



(5)

Figure 3

Aspirin's long history of use and availability without prescription diminishes its glamour compared to that of the newer NSAIDs. However, because of its low cost and long history of safety, aspirin remains the initial drug of choice for treating the majority of articular and musculoskeletal disorders. Aspirin is also the standard against which all anti-inflammatory agents are measured (Table 1). The adverse effects of aspirin–especially the gastric irritation that occurs when large doses are employed–have led to the search for alternative compounds.[8]

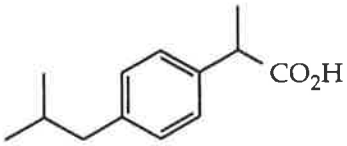
The NSAID's

Starting with ibuprofen in 1974, many classes of drugs with aspirin-like properties have been approved for use. They have a large range of chemical structures (Figure 4). Several of the propanoic acid derivatives, of which the Hamon–Massy-Westropp group is particularly interested are shown.[8]

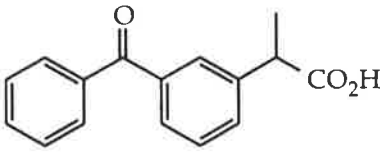
The main action of these drugs is to inhibit the production of prostanoids (by reversible inhibition of the enzyme cyclooxygenase) although they also have other actions to suppress inflammation. Cyclooxygenase (COX, prostaglandin synthase) exists in at least two isoforms: COX-1 which performs the following useful functions when activated–it catalyses the formation of (i) thromboxane A_2 (exists in platelets and promotes their aggregation and causes vascoconstriction); (ii) prostacyclin (exists in endothelium and the stomach mucosa and secrets the protective stomach lining); (iii) protaglandin E_2 (exists in the kidney and increases renal blood flow and maintains glomelar flow rate); COX-2 is induced in a number of inflammatory cells by pro-inflammatory stimuli to generate proteases, various prostaglandins and other inflammatory mediators.[7]

All the commercially available drugs in the NSAID family behave in qualitatively the same way (both with respect to their phamacologic^al actions and adverse effects), in that they are relatively non-selective inhibitors of both COX-1 and COX-2. The ideal agent would be one which selectively inhibits COX-2, and spares COX-1. There is a large amount of research by medicinal chemists to find new NSAIDs which fulfill this exigency. Luckily the two COX isoforms show only 60% homology of both their nucleic-acid and amino-acid structures, thus

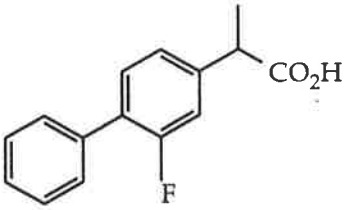
Propionic acid derivatives



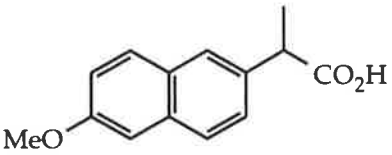
Ibuprofen



Ketoprofen

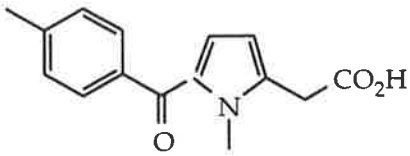


Flurbiprofen



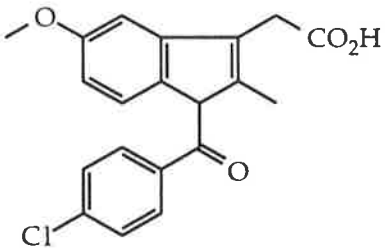
Naproxen

Pyrrolealkanoic acid derivates



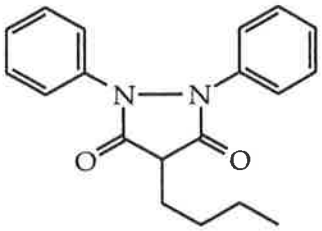
Tolmetin

Indole derivatives



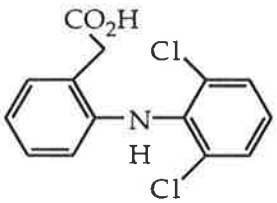
Indomethacin

Pyrazolone derivatives



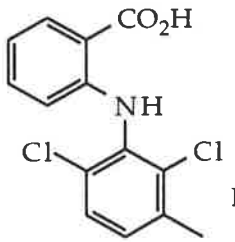
Phenylbutazone

Phenylacetic acid derivative



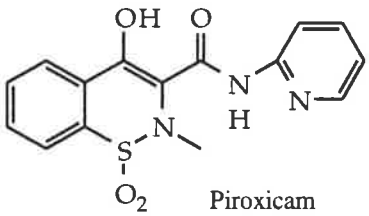
Diclofenac

Fenamate class



Meclofenamic

Oxicams



Piroxicam

Figure 4. Chemical structures of some NSAIDs.

giving the potential for selectivity of a compound for one over the other of the COX isoforms.[7]

Adverse effects of the NSAIDs occur commonly and are due to COX-1 inhibition. These involve (i) the gastrointestinal tract (gastric erosions/microbleeding, frank ulceration with haemorrhage, abdominal discomfort and pain); (ii) an antiplatelet effect, manifested as enhanced bleeding tendency; (iii) the kidney (renal impairment; salt and water retention); (iv) the respiratory system (asthma). There are also adverse effects which are much rarer and which are not related to prostaglandin inhibition. These include skin rashes; central nervous system effects such as headache, dizziness; liver damage; interstitial nephritis; blood dyscrasias. Patients with a past history of the following diseases are precluded, or much care needs to be excercised, from taking NSAIDs: peptic ulcer; renal impairment, hypertension; heart failure and asthma. Many elderly patients (a common target population for NSAIDs) fall into these categories, hence the motivation for finding new drugs which are more selective for COX-2 enteric.[7]

Asprin is unique among the NSAIDs in that it irreversibly inactivates cyclo-oxygenase by acetylation of the enzyme to form salicylic acid, which is also a NSAID. Aspirin, indomethacin and ibuprofen are much less active against COX-2 than COX-1. Indeed, the two strongest inhibitors of COX-1 are aspirin and indomethacin, the two NSAIDs which cause the most damage to the stomach. The spectrum of activities of some ten standard NSAIDs against the two enzymes ranges from a hich selectivity towards COX-1 (150-fold for aspirin) through to equi-activity on both. This range of activities nicely explains the variations in the side-effects of NSAIDs at their anti-inflammatory doses.[7,8]

There is some evidence that some patients may achieve a response to one NSAID but not to another and the most suitable agent is ascertained by trial and error. There is an increasing trend for pharmaceutical companies to develop NSAID's with long half-lives (>12 hours and often >36 hours).

The aim is to facilitate once daily administration and thus, compliance. There is little evidencce that this improves the clinical outcome, since the sojourn of the drug in the synovial fluid (inside the joint) is much longer than in the plasma. Short half-life NSAID's (e.g. ibuprofen, diclofenac, ketoprofen) can be administered twice daily with good clinical effect,

Drug	Total Daily Dose for Rheumatoid Arthritis (mg)	Recommended Number of Divided Daily Doses	Plasma Half-Life (hr)
Aspirin	4000	3	12
Diclofenac	200-300	4	1-2
Fenoprofen	2400	4	2
Flurbiprofen	200	3	3
Ibuprofen	2400	4	2
Indomethacin	150-200	3	5
Ketoprofen	200	3	1.5
Naproxen	750	2	13
Piroxicam	20	1	45
Tolmetin	1600	4	1

Table 1

despite a half-life as short as 2 hours. There is the impression that the long half-life agents (e.g. piroxicam, naproxen) may be more troublesome in the event of adverse effects, since time to clear the NSAID from the body will be longer than for a short half-life drug (Table 1).[8]

There is no evidence that these drugs alter the course of an arthritic disorder–their main effect is symptom relief. Drugs used to slow disease progression include gold based complexes and methotrexate. Adverse effects are troublesome and the agent takes weeks or months before positive effects are seen.[7]

Review of Methods Used in Asymmetric Synthesis of α-Arylpropanoic Acids[9]

A retrosynthetic analysis of the asymmetric molecule shown in Figure 5 shows the asymmetric reactions that can generate the desired chiral center.

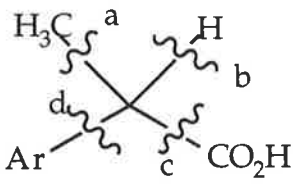


Figure 5

a) The methyl group could be introduced by asymmetric methylation of an arylacetic acid.

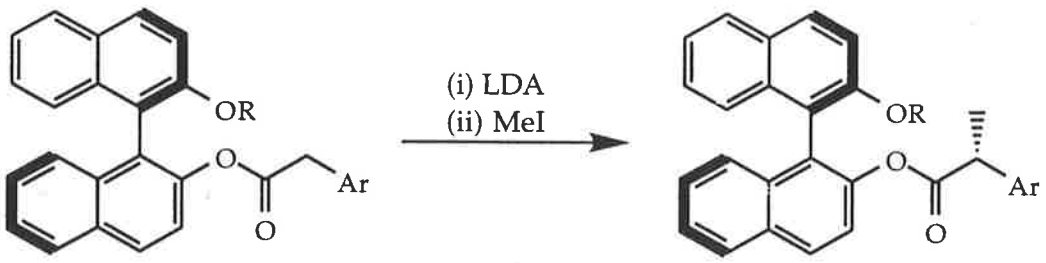
b) The C-H bond could be formed by various reactions, for example by stereoselective protonation of a ketene or addition of hydrogen.

c) α-Methyl styrene derivatives could be hydroformylated/ hydrocarboxylated.

d) The aryl-C2 bond could be formed by electrophilic substitution.[6]

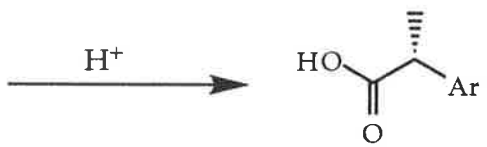
Some examples of each of these methods are discussed below.

Atropisomers of binaphthols are finding extensive use in industry as chiral auxilliaries. Fuji[10] has stereoselectively methylated the binaphthol arylacetic acid ester (6). The corresponding arylpropanoic acids were obtained on acid hydrolysis of the adduct (7) (Scheme 2).



(6i), R = H
(6ii), R = CH_3

(7i), R = H
(7ii), R = CH_3



Scheme 2

A modest diastereomeric excess of 72% was obtained from the binaphthol containing the free phenolic hydroxyl group (6i) whereas in the case of the methylated phenol (6ii) no stereoselectivity was observed. This has been explained in terms of the possible conformations of the enolates. The *Z* enolate is formed exclusively on deprotonation of the ester with LDA in the solvent system THF/HMPA. It can be seen (Figure 6) that the two naphthyl rings bisect each other at a torsional angle of about 90° due to steric factors and electrostatic repulsion keeping the negatively charged oxygens maximally apart. Thus, the *re*-face of the nucleophilic carbon is more open for alkylation, when *(R)*-binaphthol is used as a chiral auxiliary. On the contrary, such a face discrimination is reduced in methylated phenol (Figure 7) allowing freer rotation about the aryl-O bond resulting in reduced diastereoselectivity. Alkylation with the more bulky isopropyl and *t*-butyl iodides gave a higher selectivity but this is not relevant to arylpropanoic acids.

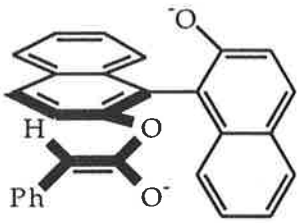


Figure 6

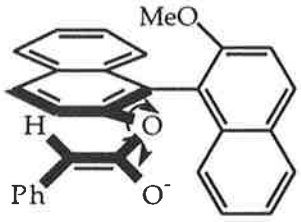
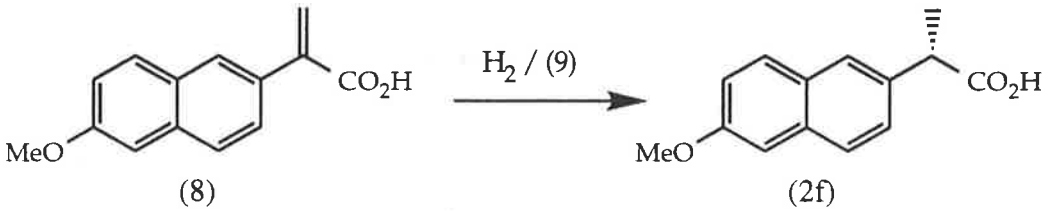


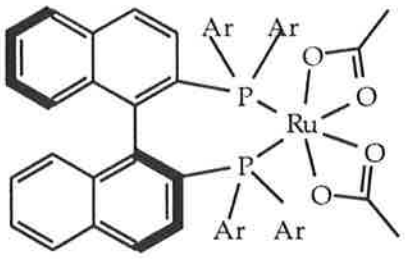
Figure 7

Noyori[11] has synthesized *(S)*-naproxen with an enantiomeric excess of 97% in good chemical yield by homogeneous hydrogenation of the olefin (8) using the chiral phosphine ruthenium complex (9) (Scheme 3). The reactive intermediate proposed co-ordinates the alkene double bond and the carboxylate to the Ru-metal center and the extent of asymmetric induction is dependent on the substitution pattern and the reaction conditions, particularly, the hydrogen pressure.



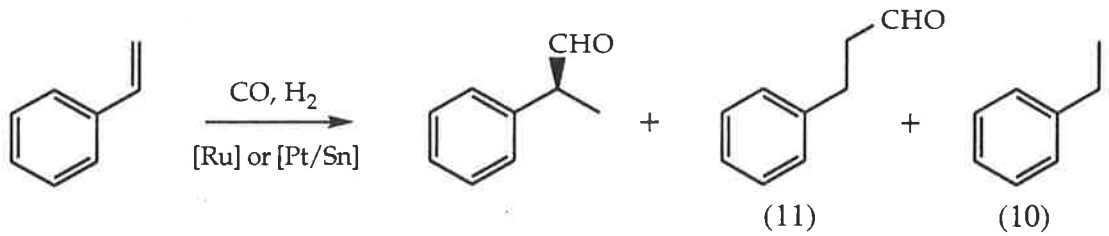
(8) (2f)

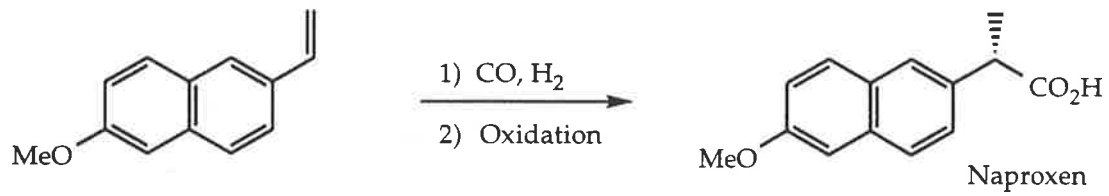
Scheme 3 (catalyst (9) over page)



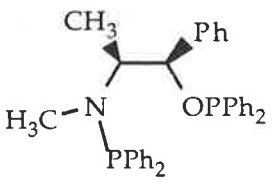
(9)

Hydroformylation[12] (and hydrocarboxylation) of olefins are examples of the third type of reaction where asymmetric hydroformylation followed by oxidation provides a straightforward route to arylpropanoic acids (Scheme 4). Despite decades of research the hydroformylation reaction remains problematical with poor chemical yields and/or optical purities. Chemoselectivity is a problem with hydrogenation of double bonds taking place, e.g. giving (10); problems of regioselectivity occur since the reaction involves addition to the non-symmetrical double bond, e.g. giving (11), and problems of stereoselectivity related to the efficiency of the transfer of the chiral information from the catalysts to the substrate. The use of a rhodium complex provides high conversions and high branched selectivities but the highest e.e. obtainable is 31% using the phosphine ligand *(R, S)*-EPHOS (Figure 8).[13] Contrariwise the use of platinum based catalyst gives consitently higher stereoselectivities but the chemical yields of the branched aldehyde are always unsatisfactory.





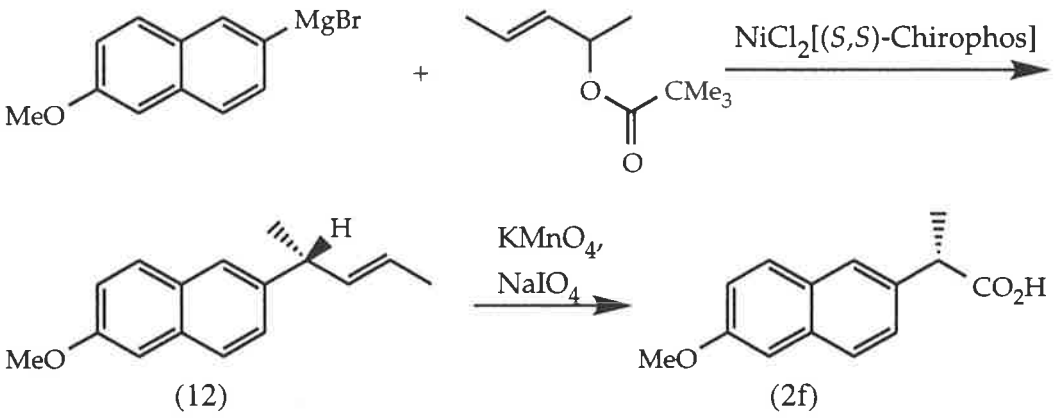
Scheme 4



EPHOS

Figure 8

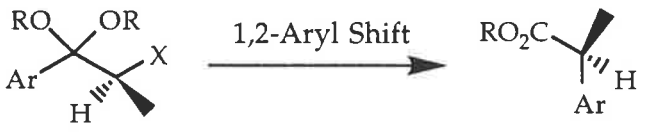
The fourth type of synthesis involves the formation of the aryl-aliphatic C-C bond by reaction of a nucleophilic aromatic moiety with an electrophilic alkyl moiety or vice versa. An example of the former type by Hiyama and Wakasa[14] reacts 6-methoxy-2-naphthyl magnesium bromide with 3-penten-2-yl pivalate using $NiCl_2$[(-)-(2*S*,3*S*)-2,3-bis(diphenylphosphino)butane] as a catalyst (abbreviated as $NiCl_2$[(*S*,*S*)-chiraphos]) afforded (*R*)-4-(6-methoxy-2-naphthyl)-1-butene (12). Oxidative cleavage of the double bond led to naproxen (2f) in a low optical purity of 64% (Scheme 5).



(12) (2f)

Scheme 5

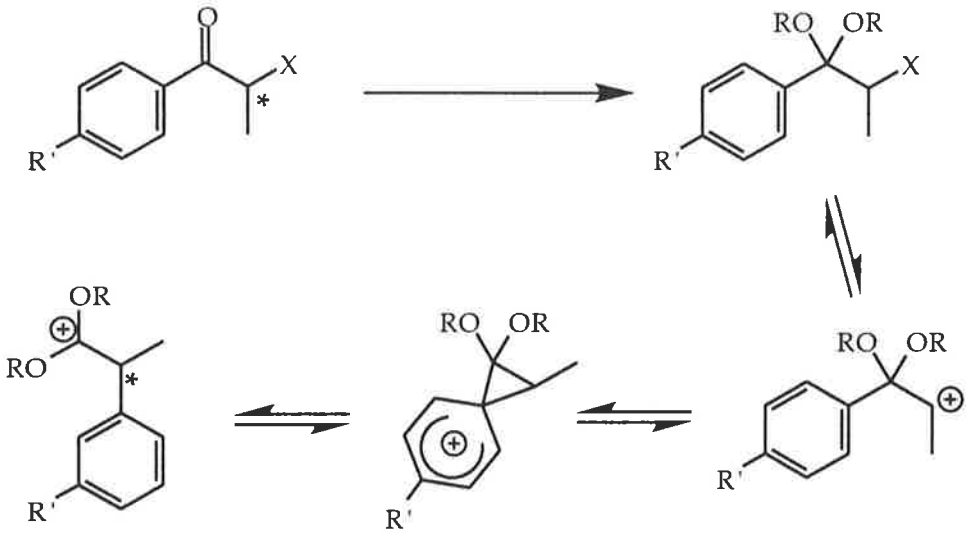
A method for the synthesis of optically active α-arylpropanoic acids, different than those based on the introduction of one of the four groups forming the chiral center, employs the 1,2-aryl rearrangement[15,16] and is both simple and cost effective. The intermediate which undergoes rearrangement is of the general type (13) where X is a leaving group such as a halogen or sulphonate and the migration is facilitated by a Lewis acid (Scheme 6). The reaction proceeds with complete inversion of configuration giving the product with no loss of optical purity.



(13)

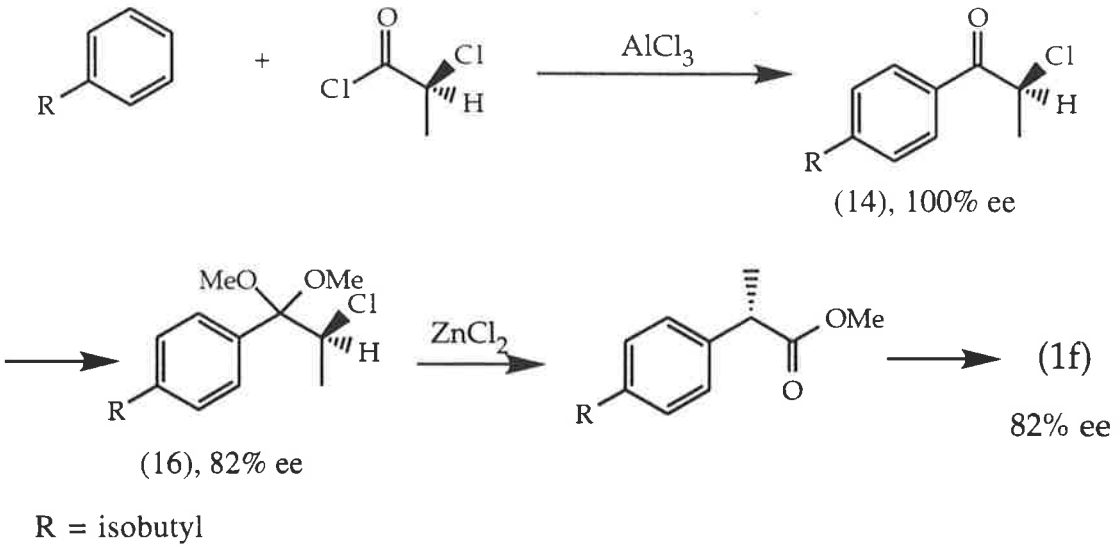
Scheme 6

As the mechanism involves a cyclopropyl-like transition state, the precursory ketones, having an sp^2 carbon which would restrict the attainment of such a state are to be converted to the corresponding acetals which have sp^3 geometry. A Lewis acid activates the carbon-halogen bond giving a carbonium ion which is destabilised relative to the highly stabilised oxonium ion. Electron withdrawing groups decrease and electron donating groups increase the reaction rate, a fact which supports the hypothesis of the inclusion of the aryl ring in the transition state (Scheme 7). The most important aspect of this rearrangement is its complete stereospecificity, so the optical purity of the product is dependent on the purity of the acetal substrate.

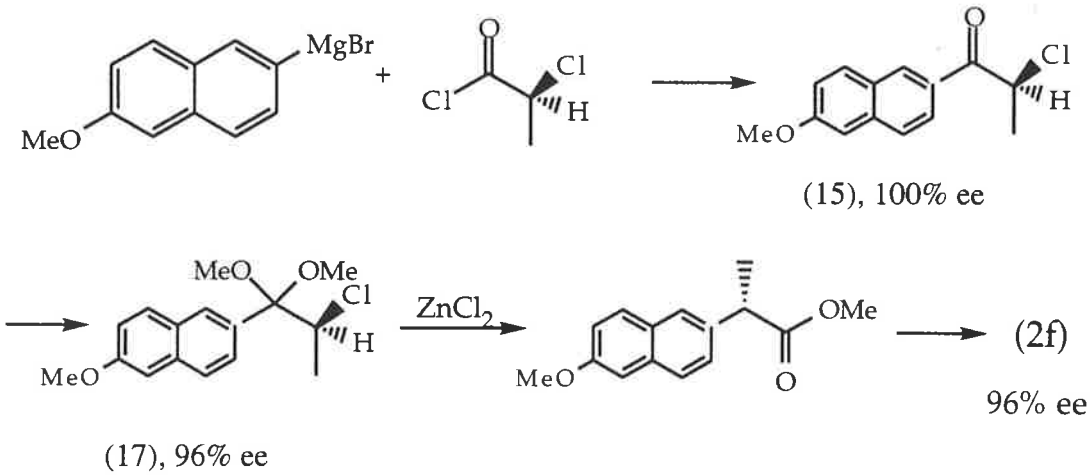


Scheme 7

As an example Picolo[17] has prepared optically active ibuprofen (Scheme 8) and naproxen (Scheme 9) by $ZnCl_2$-catalysed rearrangement of the corresponding optically active α-chloro acetals. The optically pure α-halo ketones (14) and (15) were obtained by acylation of isobutylbenzene and 6-methoxynaphthyl-2-magnesium bromide respectively. The acylating agent, optically pure α-chloropropionyl chloride, was derived from (*S*)-alanine. Some partial racemisation occurred in both series during the formation of the acetal, (16) having an e.e. of 82% and the naphthyl derivative (17) having an optical purity of 96%. In each case these were the purities seen in the final product acids.



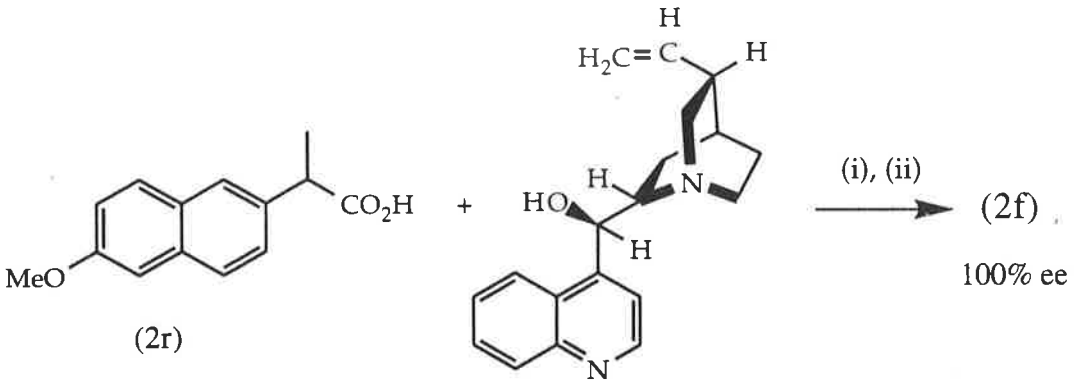
Scheme 8



Scheme 9

The classical approach of obtaining enantiomerically pure compounds by resolution of the racemate has been used to obtain optically pure naproxen which was the first of the NSAIDs to be marketed in enantiomerically pure form. Due to the development of efficient methodologies for asymmetric synthesis this technique is losing practical importance.

Harrison[18] reacted (-)-cinchonidine with racemic naproxen to obtain a diastereomeric mixture of salts, of which repeated recrystallization furnished the less soluble isomer. HCl treatment of this pure diastereomeric salt liberated optically pure naproxen (Scheme 10).



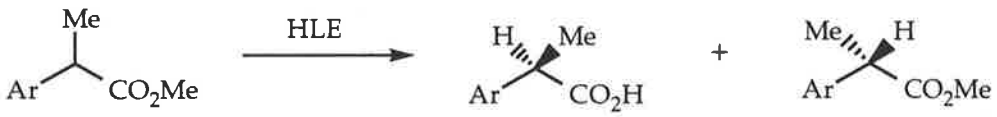
(2r)

(-)-cinchonidine

(i) 2 * recrystallisation
(ii) HCl

Scheme 10

Enzymatic resolution has been used by Bloch[19] to obtain both the enantiomers of naproxen. The enzyme *Horse liver esterase* (HLE), used as its inexpensive and commercial acetone powder, catalyzed the selective hydrolysis of the ester (18r) to afford the acid (1f) and the unreacted ester (18g) which are readily separable. The later is then hydrolysed to the acid (1g) (Scheme 11).



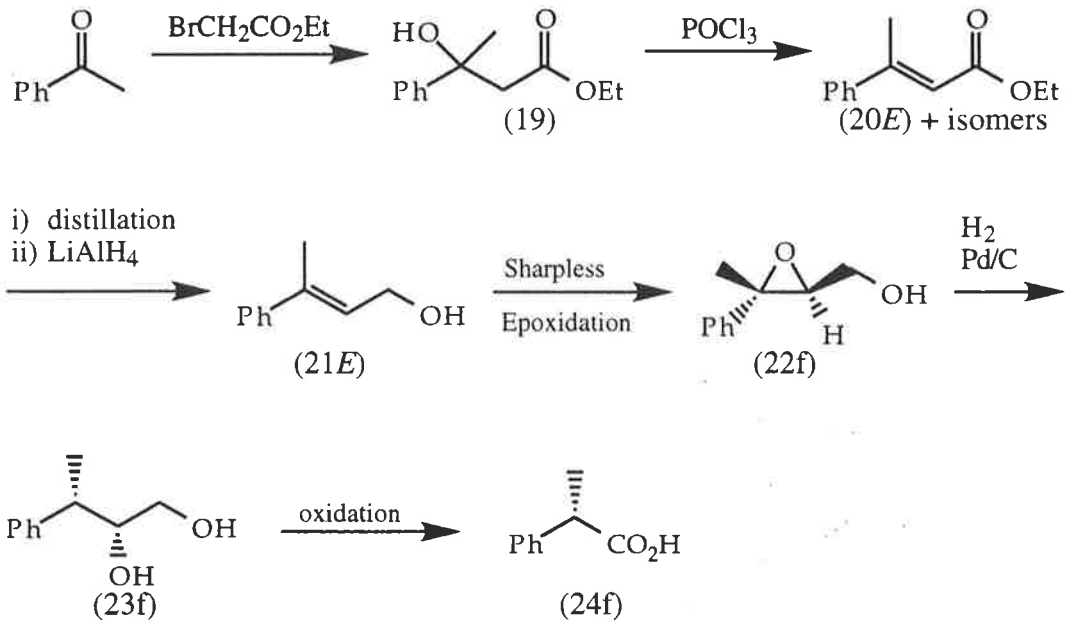
(18r) (1f) (18g)

Ar = 4-isobutylphenyl

Scheme 11

Review of Work in the Hamon–Massy-Westropp Group

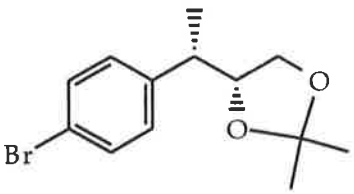
The initial exploratory work on which this thesis is based was performed by Coghlan, Slobedman and Hecker.[20] The main features of this method of obtaining the optically active propanoic acid side chain are the Sharpless epoxidation to introduce the optical activity and a stereospecific hydrogenolysis of this epoxide (Scheme 12).



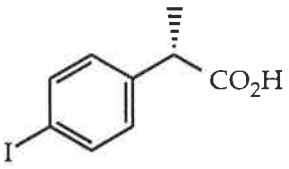
Scheme 12

Acetophenone reacted with ethyl bromoacetate in the Reformatsky reaction to give the alcohol (19) which was dehydrated to give a mixture of unsaturated esters. These were separated by fractional distillation to give the configurationally pure ester (20*E*). This was reduced with lithium aluminium hydride to give allylic alcohol (21*E*) which is the substrate for the Sharpless epoxidation. The enantioselective expoxidation gives the optically active epoxide (22f) which was stereo- and regioselectively hydrogenolysed over palladium on carbon catalyst to the diol (23f). Chromatography provided the pure diol which was oxidatively cleaved to the optically pure acid (24f) with sodium periodate and ruthenium tetroxide.

Using the above route as a skeleton Newton[21,22] has demonstrated the possibility of obtaining access to a variety of 2-arylpropanoic acids via common optically active precursors. This was done in both the *meta* and *para* series. Such a route would be particularly useful should the preparation of new compounds for biological screening be required. For initial investigations the optically active bromo acetonide (33f) was synthesized (Figure 9) to which the *iso*-butyl group was coupled to make ibuprofen. The optically active intermediate acid (37f) (Figure 9) was subsequently made, which is closer, structure-wise, to the final 2-arylpropanoic acid sought. The outline syntheses concerning these common intermediates will now be discussed.



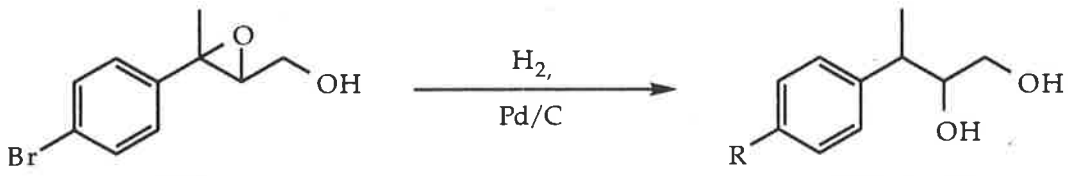
(33f)



(37f)

Figure 9

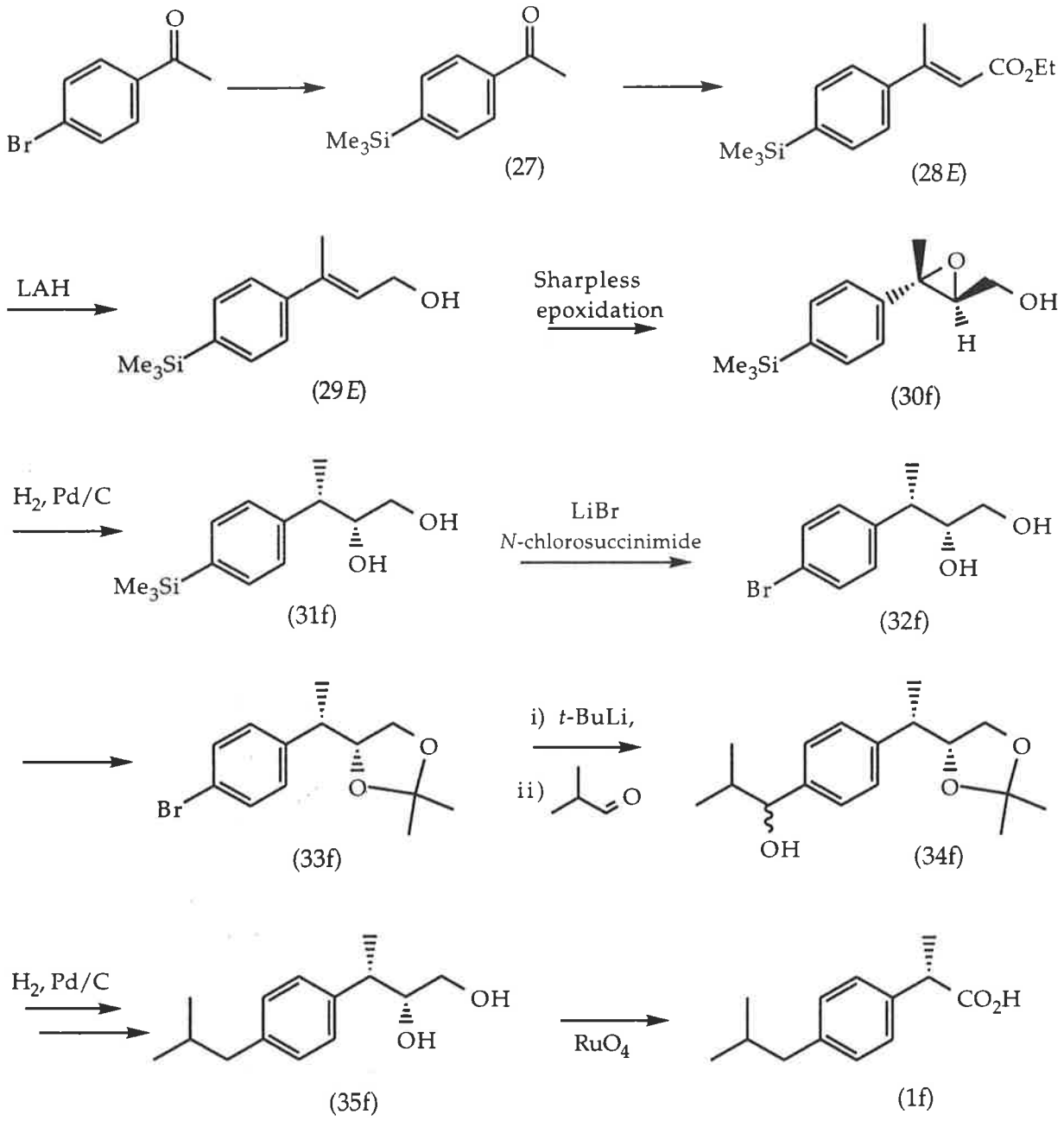
Initially the bromo derivative of (23), the diol (26), was sought, however loss of bromine occurs more readily than cleavage of the epoxide ring in hydrogenolysis of the bromo epoxide (25) (Scheme 13) and the compound (23) was obtained under these conditions. Replacement of bromine in *p*-bromoacetophenone with the trimethylsilyl group to give the silyl arene (27) (Scheme 14) proved to be one way around this problem.



(25)

(26) R= Br,
(23) R= H

Scheme 13



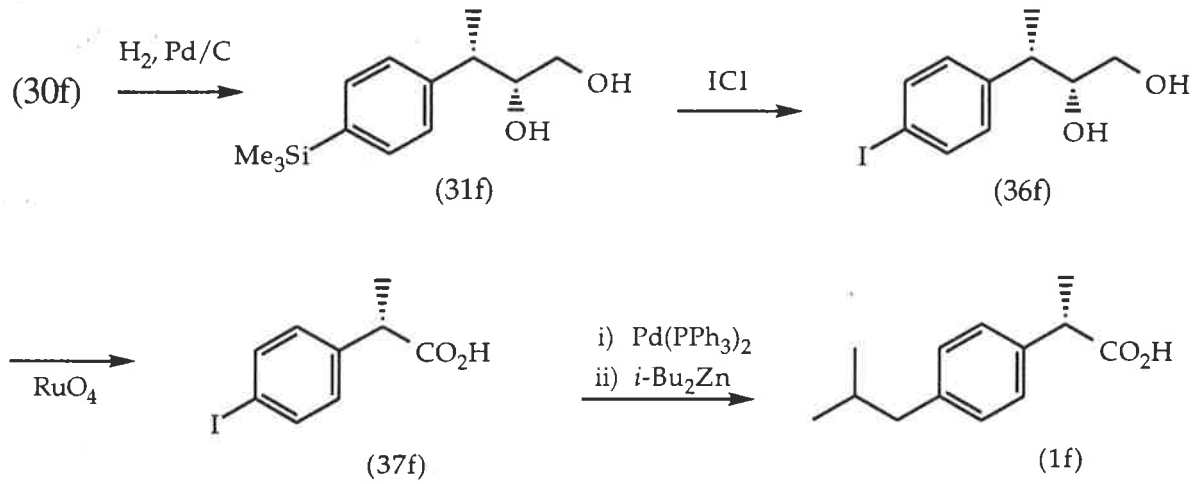
Scheme 14

It was necessary to first protect the ketone as an acetal before generation of a Grignard reagent which reacted with trimethylsilylchloride. Reaction of the ketone (27) then gave mainly the unsaturated ester (28*E*) in the Wittig reaction, the crude mixture of which was reduced to the allylic alcohol (29*E*). The Sharpless asymmetric epoxidation furnished the optically active epoxide which was purified by chromatography and recrystallized to give the single enantiomer (30f). This underwent stereoselective hydrogenolysis of the epoxide ring with retention of the silyl group to give the diol (31f) which was determined to have a d.e. of 99%+. The silyl

group was replaced with bromine to give the diol (32), which was protected as the acetonide (33). A metal halogen exchange reaction was employed to incorporate the *iso*-butyl substituent to give the alcohol (34) which was hydrogenolysed and deprotected to the penultimate product (35). Oxidation with periodate and catalytic ruthenium tetroxide gave ibuprofen (1f) which was determined to have an optical purity of 96%.

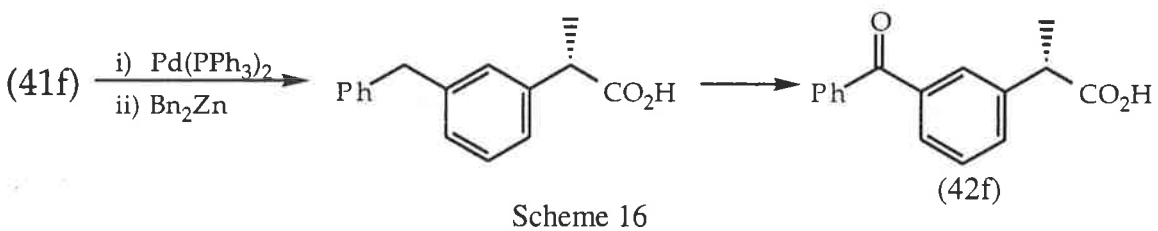
Next, an intermediate was found by Newton[22] that would give access to a large range of 2-arylpropanoic acids. The iodo acid (37f) (Scheme 15) was synthesized for this purpose; this has the optically active propanoic acid moiety in place and the aryl ring activated to coupling reactions. This means that the aryl substituent can be introduced as the final step in the synthesis, which enables oxidation sensitive side chains to be incorporated (Scheme 17).

The trimethylsilyl diol (31f) was converted to the iodo diol (36f) by reaction with iodine monochloride and this was oxidized to the acid (37f) with ruthenium tetroxide catalyst (Scheme 15).



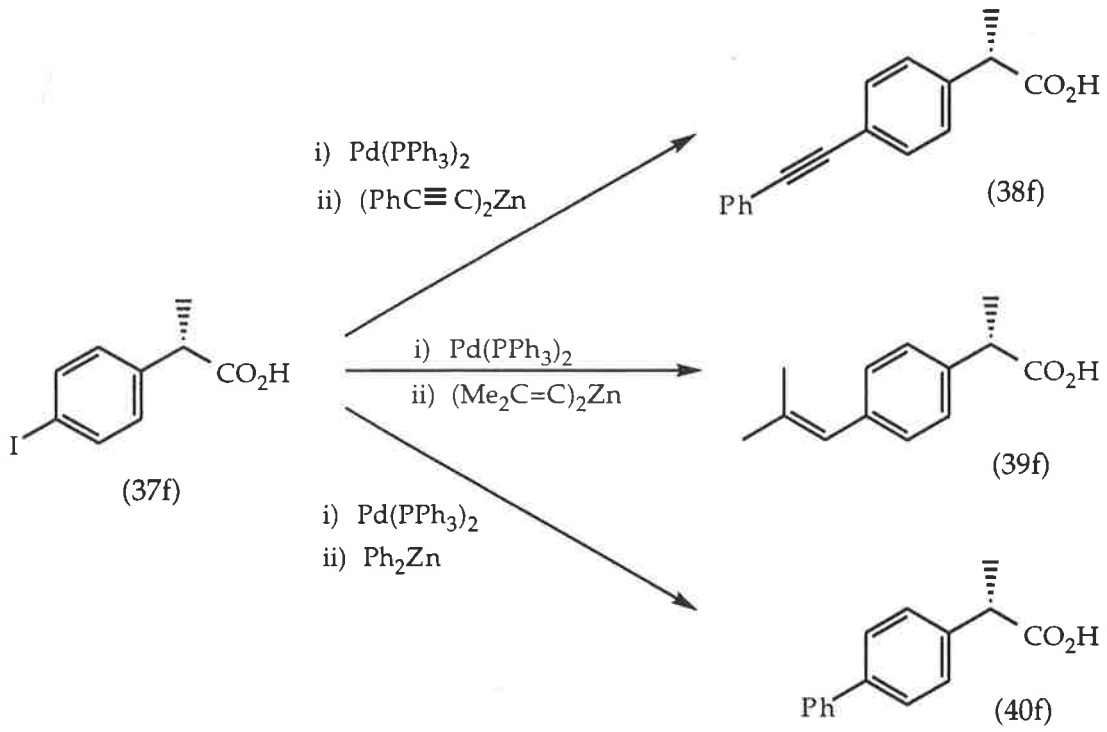
Scheme 15

The corresponding *meta* substituted iodoacid (41f) was coupled with dibenzyl zinc, the product of which, on oxidation gave ketoprofen (42f) an important profen drug (Scheme 16).[21]



Scheme 16

The iodo acid (37f) was then coupled using a palladium(0) catalyst with an alkyl (*iso*-butylzinc) group to give ibuprofen (1f); with an alkynyl (phenylethynylzinc) group to give the acid (38f) (Scheme 17); with an alkenyl (*iso*-butenylzinc) group to give the acid (39f); and with phenylzinc to give the acid (40f).

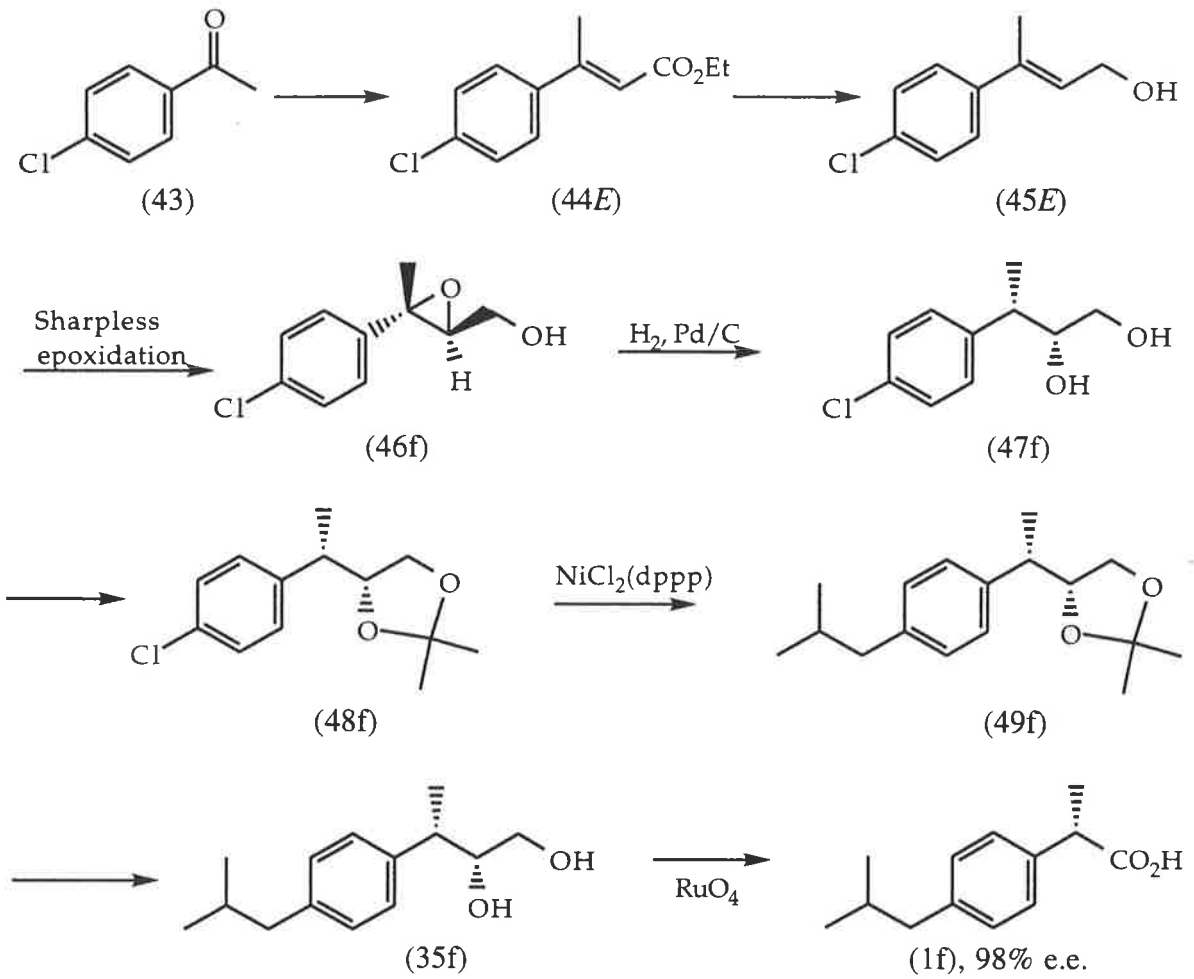


Scheme 17

A piece of work performed in Honours by the author (which predates the route to the iodo acid (37f)), the synthesis of optically pure ibuprofen, attempted to find a shorter, more efficient route to a common optically active intermediate. Since it was found that hydrogenolysis of the bromo group occurred in both the *meta* and *para* (25) compounds, attention was turned to the corresponding chloro compound. The chloro group was used to functionalize the arene, and it was hoped that this group would not be hydrogenolysed and also that it could be coupled with sufficient ease to a variety of organic side chains.

Thus, during the Honours project *p*-chloroacetophenone (43) was used to form the αβ-unsaturated ester mixture (44*E*) and (44*Z*), which was reduced to the mixture of allylic alcohols

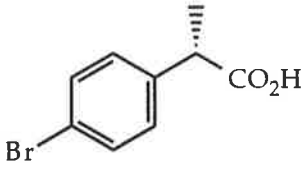
(45*E*) and (45*Z*) (Scheme 18). Sharpless epoxidation gave the expected mixture of enantiomers, and recrystallization furnished the pure isomer (46f) with a stereopurity of 98%+. This was hydrogenolysed to the single diastereomer (47f) with retention of the chloro group. Protection of the diol as the acetonide (48f) gave the intermediate which was coupled with the *iso*-butyl group using nickel catalysed coupling.[23] This step was grossly inefficient, an almost stoichiometric amount of 60% of the Ni catalyst was required before complete conversion to the coupled product (49f) was effected. Kumada[23] has performed coupling reactions, using simpler chloro arenes, with 2-3% of this catalyst. The last step, oxidation to ibuprofen, was performed catalytically with RuO_4 to give ibuprofen with an optical purity of 98%.



Scheme 18

Although ibuprofen has been prepared by this route, due to the problems encountered in the coupling step, the intermediate (48f) is not really satisfactory for its intended purpose and therefore an alternate route was planned.

Chapter 1 of this thesis discusses a new route to the bromo compound (50f), related to the iodo acid (37f), which it was envisioned could be coupled more readily in similar ways to that achieved with the iodo acid.



(50f)

The key, stereoselective reactions used in this synthesis are the Sharpless asymmetric epoxidation and the Ti(O-*i*-Pr)$_4$ mediated S_N2 ring opening of the product epoxides and as such they deserve further discusion.

Sharpless Asymmetric epoxidation

This titanium-tartrate mediated epoxidation of prochiral allylic alcohols by alkyl hydroperoxides gives excellent enantioselectivity and can be applied to many substrates. An advantage of the reaction is that the stereochemistry of the product can be predicted by orienting the allylic alcohol as shown in Figure 10. From this position, oxygen will be delivered from the top face if the D-(-)-tartrate is used and from the bottom face if the L-(+)-tartrate is used.[27] The product epoxides are versatile and important intermediates in organic chemistry. The strain of the three-membered ring makes them accessible to a large variety of reagents. There are several reviews dealing with the Sharpless epoxidation.[24-27]

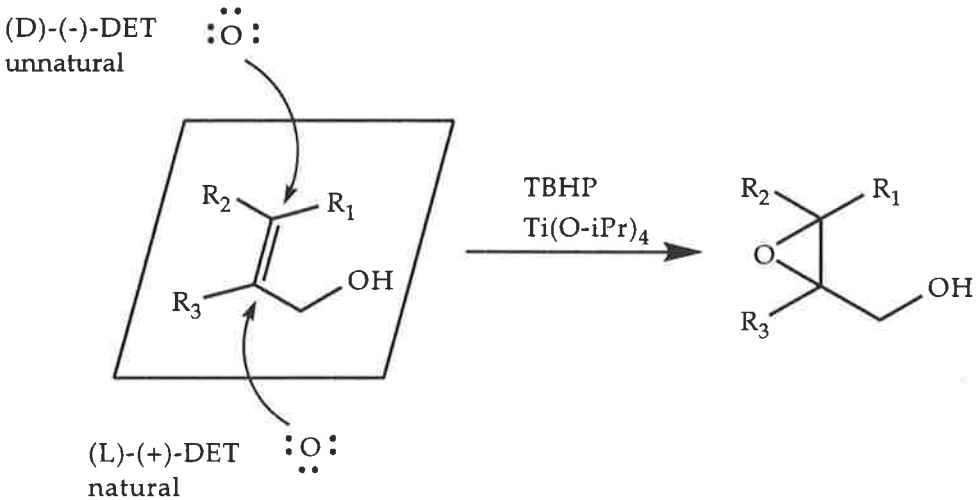
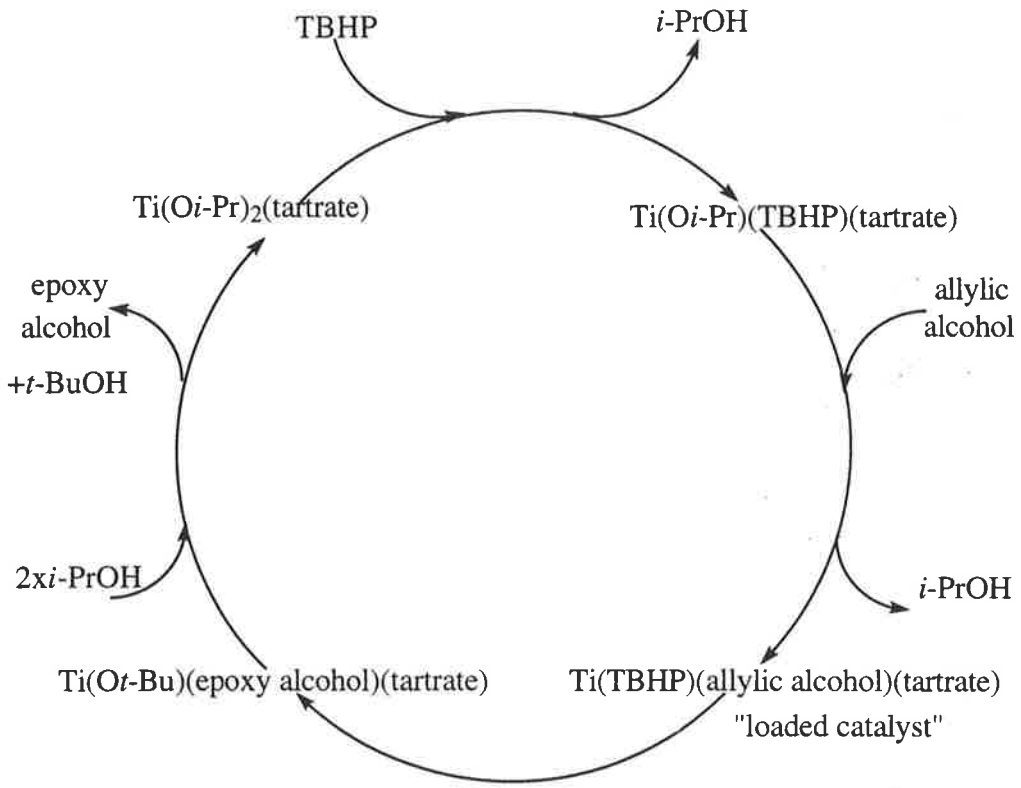


Figure 10

The catalytic coordination complex is based on titanium(IV), which rapidly exchanges alkoxide ligands in solution. The optically pure tartrate ligand readily displaces the propoxide ligands as it is bidentate and as such forms a more stable structure than the monodentate propoxide complex, which is then ready to receive the substrate and reagent (Scheme 19a).

$$Ti(O\textit{i}\text{-}Pr)_4 + \text{tartrate} \rightleftharpoons Ti(O\textit{i}\text{-}Pr)_2(\text{tartrate}) + 2\ \textit{i}\text{-PrOH}$$

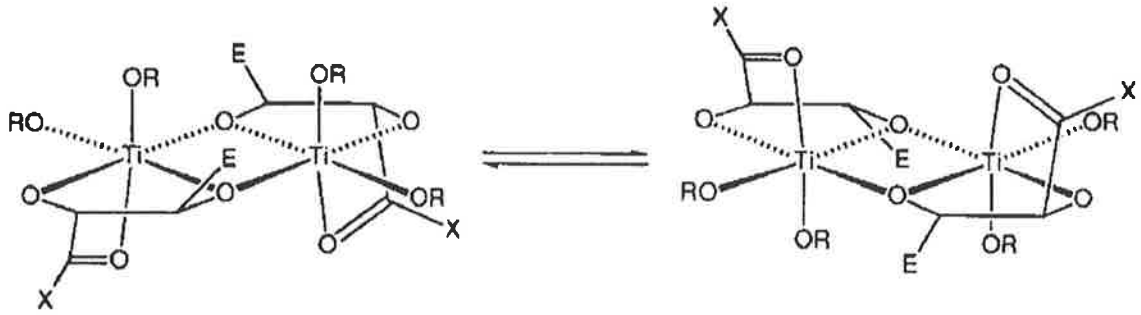
Scheme 19a



Scheme 19b

Titanium(IV) has a d^0 outer orbital and so is ~~flexible~~ variable in its co-ordination number. It rapidly and reversibly accepts TBHP and the allylic alcohol and displaces PrOH thus forming the "loaded" catalyst. Now the epoxidation occurs, with the tartrate transferring its chiral information in a highly efficient manner. The epoxide and spent reagent are released from their co-ordinated state and the regenerated catalyst is now ready for another cycle (Scheme 19b).

Crystallographic,[28] spectroscopic, and molecular weight data on closely related compounds suggest that the major species in a 1:1 titanium alkoxide–dialkyl tartrate solution is the C_2-symmetric tartrate-bridged dimer (51) with the titanium atoms in identical stereochemical environments (Figure 11). To account for the sameness of all the tartrate ester groups in the room temperature NMR spectrum, a fluxional equilibrium between the two structurally degenerate complexes has been proposed.[27]



(51)

Figure 11

Mechanistic findings strongly imply that this major species (51) is the catalytically active species. In the roughly octahedral, reactive catalyst species, the allylic alkoxide is believed to be bound *trans* to the co-ordinated ester carbonyl and the *tert*-butyl peroxide *cis* to the carbonyl. S_N2-type attack of the olefin π-bond along the O-O bond axis results in rate-determining oxygen atom transfer (Figure 12).

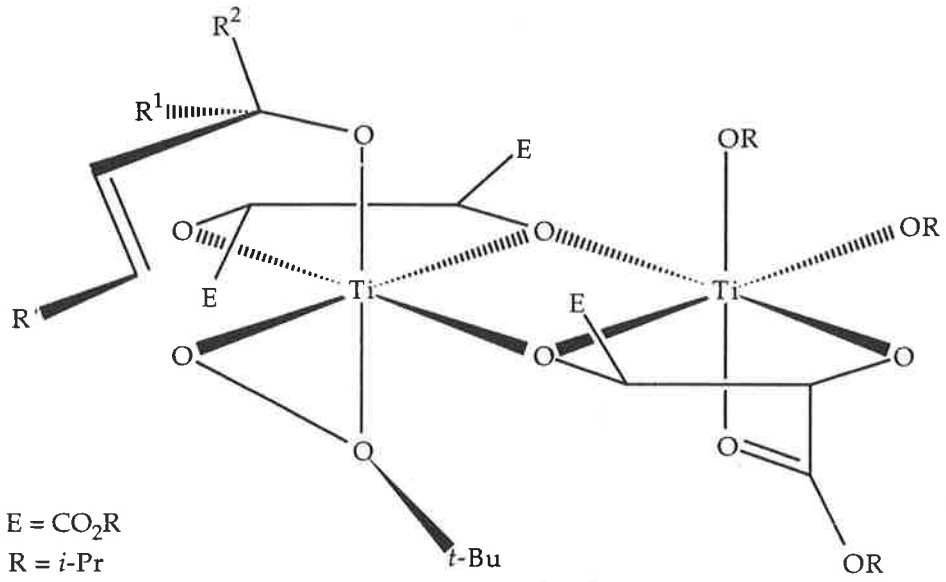


Figure 12

An alternate mechanism invoking an ion-pair transition state assembly has been proposed by Corey[29] which has however been discounted as incorrect by Sharpless based on inconsistency with kinetic data.

Regio- and Stereoselective Epoxide Opening

2,3-Epoxy alcohols can be opened regioselectively by nucleophiles with the use of $Ti(O\text{-}i\text{-}Pr)_4$ under mild conditions.[30,31] Based on knowledge of the titanium-catalysed asymmetric epoxidation, the complex shown in Figure 13, which holds the epoxide in a bidentate manner, was invoked. The titanium alkoxide is a weak Lewis acid and the epoxides are weak Lewis bases, this causes the C-O bonds to weaken, particularly the C3-O bond, which is then more susceptible to nucleophilic attack, the products being a mixture of regioisomers (Scheme 20). The regioselectivity (C-3/C-2) is dependent on several factors including the type of nucleophile, with the 'softer' nucleophiles being the least regioselective. The solvent used also affects the regioselectivity, with a complexing solvent such as THF giving a poorer selectivity, as the epoxide is less strongly bound to the Ti centre, while benzene causes the selectivity to be greater, being a non-coordinating solvent.[32]

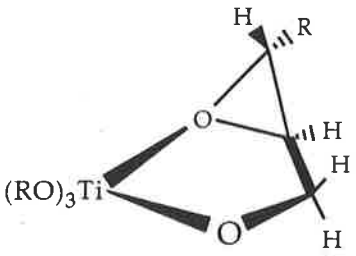
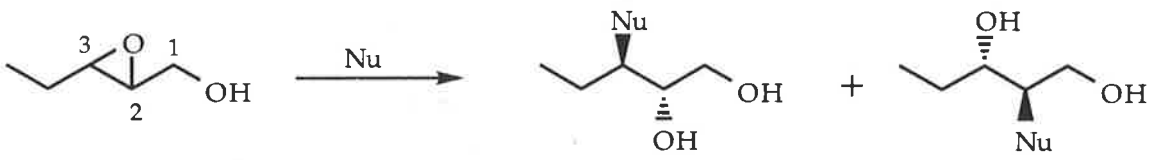


Figure 13

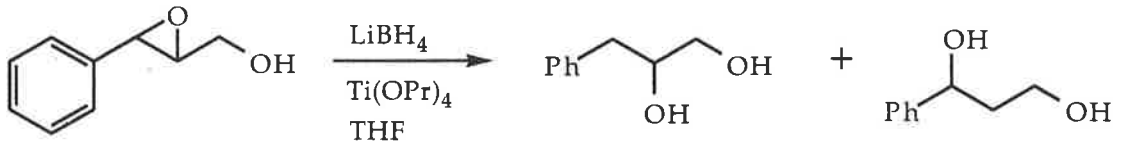


C-3 opening C-2 opening

Scheme 20

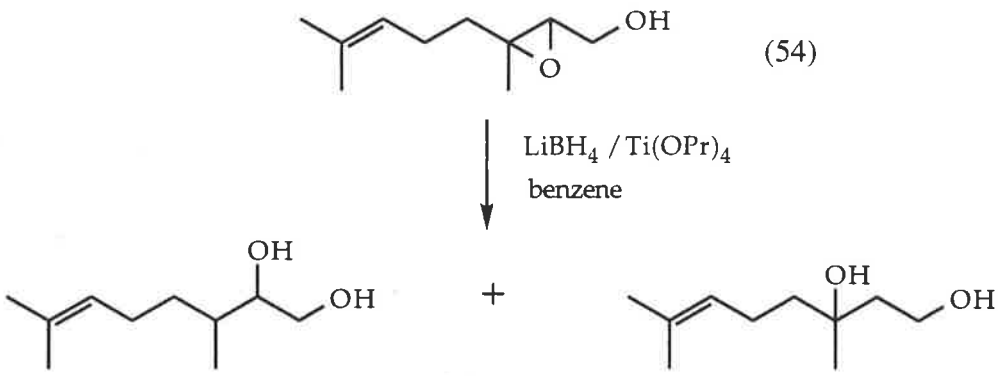
Dai[32] has performed a regioselective reductive epoxide opening on the epoxy alcohol (52) to give a mixture of regioisomers, 1,2-diol : 1,3-diol with a selectivity of 54:1 (Scheme 21). The nucleophilic species here is borohydride and the 1,2-diol (53) is the desired isomer. A system that is ~~tertiary at the~~ at the tertiary benzylic position (as will be the system that will be explored in the current work) might be more selective than is the aliphatic epoxide (54) (Scheme 22). The regioselectivity of the reduction of this sterically hindered epoxide is much poorer.

This reduction accomplishes a similar result to that obtained by the catalytic hydrogenolysis reaction with the following differences in selectivities: i) the regioselectivity is often much poorer, ii) the chemoselectivity difference relevant to this thesis is that the hydrogenolysis reaction reduces the aryl-halogen bond whereas the hydride reduction does not, and iii) the stereoselectivity is equally high in both reactions.



(52) (53) 54 : 1

Scheme 21



6.8 : 1

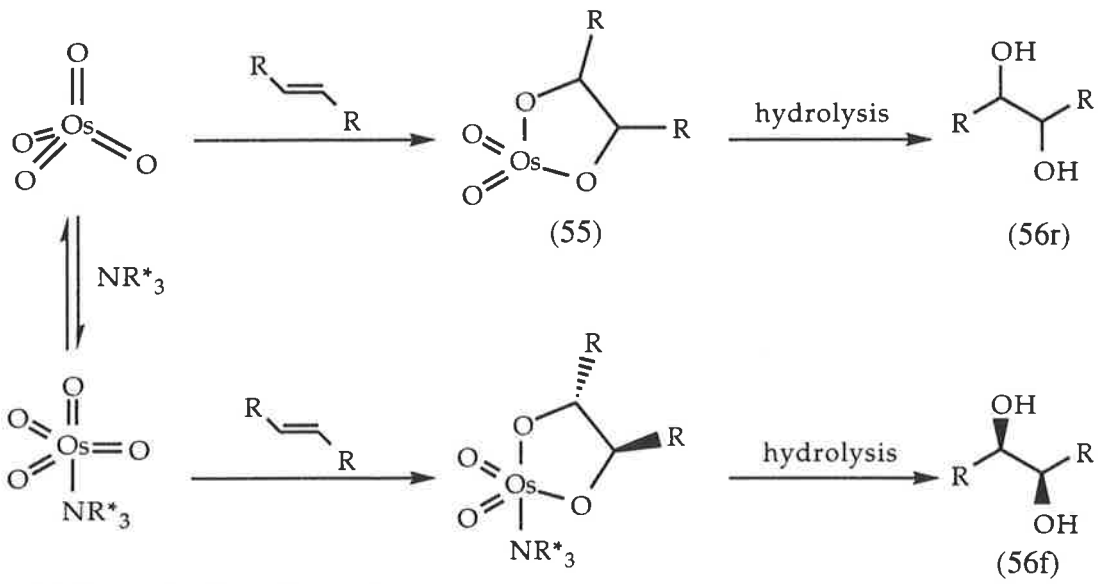
Scheme 22

The Sharpless asymmetric dihydroxylation and catalytic hydrogenolysis were used in later syntheses of naproxen and attempted synthesis of ketorolac and are also discussed. The reaction schemes that were planned for these two drugs are described in chapters 2 and 3.

Sharpless Asymmetric Dihydroxylation

The osmium catalysed asymmetric dihydroxylation (AD)[33-35] is more general than the titanium-mediated asymmetric epoxidation as it does not require a coordinating hydroxyl group.

In the stoichiometric reaction of osmium tetroxide, the olefin is first osmylated to form an osmium(VI) monoglycolate ester (55) which is hydrolysed to the racemic diol (56r) and an osmium(VI) species (Scheme 23).[33] Osmylation can be accelerated by addition of pyridine[36] or other tertiary amines, and this results in asymmetric induction in the hydrolysed diol (56f) when the amine is optically active. Inclusion in the reaction of a co-oxidant serves to return the osmium to the osmium tetroxide level of oxidation and allows for the use of osmium in catalytic amounts. Co-oxidants that minimize over-oxidation are alkaline *t*-butylhydroperoxide, *N*-methyl-morpholine-*N*-oxide and the important potassium ferricyanide.

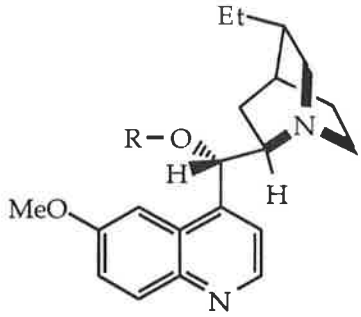


NR^*_3 = optically active amine

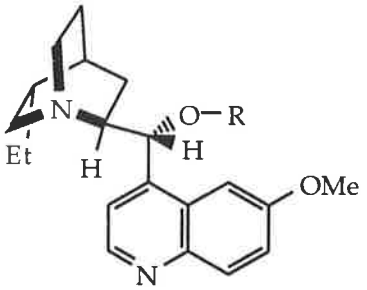
Scheme 23

Based on selection of ligand (Figure 14) enantioselectivities of greater than 95% are achievable for many alkenes. Sharpless[37] found in 1980 that osmylation of olefins in the presence of the acetate derivatives (58f) and (58'g) of dihydroquinidine [DHQD (57f)] and dihydroquinine [DHQ (57'g)], under stoichiometric conditions gave, after hydrolysis of the osmate ester, optically active diols with 25-29% ee. (57f) and (57'g) are regioisomers because of the

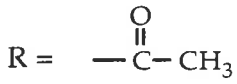
difference in attachment of the ethyl group, however they operate like enantiomers in the AD reaction and have been called "pseudoenantiomers" for this reason. More than 250 derivatives, mainly of the cinchona alkaloids, have been made and tested as chiral ligands in the catalytic AD process. A recently discovered pair of ligands, the bis-DHQD and bis-DHQ ethers of phthalazine-1,4-diol (60f) and (60'g) give the highest optical purities. Similarly as for the asymmetric epoxidation the stereochemistry of the product diol can be predicted before the reaction is performed, based on the sizes of the olefinic groups and the placement of this in an empirically determined jig.[33]



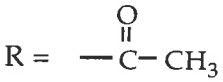
R = H (DHQD) (57f)



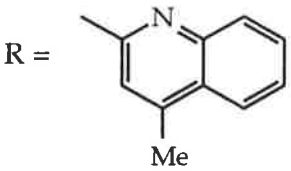
R = H (DHQ) (57'g)



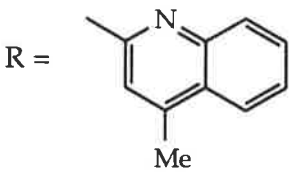
(DHQD-OAc) (58f)



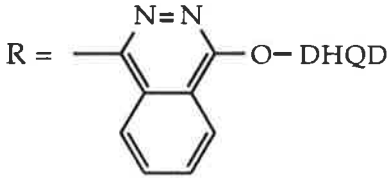
(DHQ-OAc) (58'g)



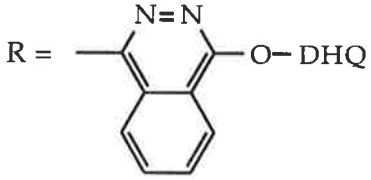
(DHQD-MEQ) (59f)



(DHQ-MEQ) (59'g)



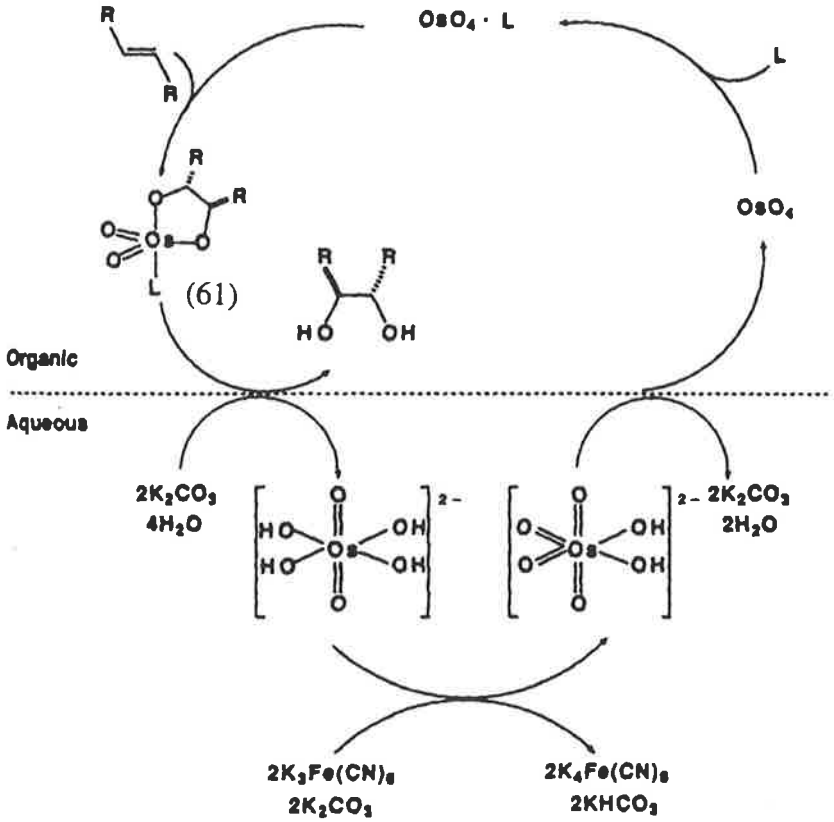
$(DHQD)_2$-PHAL (60f)



$(DHQ)_2$-PHAL (60'g)

Figure 14

Catalytic ADs are easier reactions to perform than Sharpless epoxidation reactions. The reaction actually requires water and is insensitive to oxygen and so can be carried out without regard to exposure to the atmosphere. The osmium species, as potassium osmate, chiral ligand, oxidizing agent–potassium ferrricyanide and required base potassium carbonate, are available commercially premixed. When this particular oxidizing mixture is used the reaction is carried out in a stirred mixed solvent system of *tert*-butanol and water (Scheme 24). First, osmylation of the olefin proceeds to form the osmium(VI) monoglycolate-amine complex (61). Next, at the organic-aqueous interface, hydrolysis of the glycolate ester releases the diol into the organic phase and the reduced osmium into the aqueous phase as the hydrated osmate(VI) dianion. Oxidation of osmate(VI) by potassium ferricyanide regenerates osmium tetroxide. Loss of two hydroxide groups from the perosmate(VII) ion gives osmium tetroxide, which then migrates back into the organic phase to restart the cycle.



L= optically pure amine

Scheme 24

Catalytic Hydrogenolysis

Catalytic hydrogenolysis is a powerful tool for the reductive cleavage of benzylic C-O bonds as it is often highly regio- and stereoselective and the experimental conditions are simple to apply.[38] Depending mainly on catalyst choice the product stereochemistry will either be inverted, as with Pd, or retained, as with Ni. Other factors influencing the stereochemistry are the solvent, steric factors and temperature.[39] The rate of reduction parallels the ability of the oxygen to bear a negative charge and increased in the order OH < O-alkyl < O-aryl < OH^+-alkyl < OH_2^+ < OAc < $OCOCF_3$.[38] Epoxides are also readily cleaved as the release of ring strain is large.

Conditions used to cleave the C-O bond also affect aryl halogen bonds. The order of halogen loss is I>Br>Cl>F.[40] This was the cause of a major obstacle for the current work where attempts were made to find conditions which stereoselectively cleave the epoxide leaving the arene-bromo group intact. This has been done by catalytic hydrogenolysis when the aryl halogen was chlorine and achieved without the use of catalytic hydrogenolysis for the corresponding bromoarene by nucleophilic substitution.

The general finding of the stereochemical outcome of hydrogenolysis of benzyl alcohols and ethers depends primarily on the catalyst. The hydrogenolysis proceeds with retention on Ni, Co and Cu catalysts, and with inversion on Pt and Pd catalysts. From this it has been suggested by Esashi[41] that the hydrogenolysis proceeds through sterically different chemisorbed states of substrates which depend on the kind of catalyst metal. Esashi has shown that stereoselectivity is independent of the kind of atmosphere. Thus hydrogenolysis over palladium presorbed with hydrogen and under helium atmosphere proceeded with stereospecific inversion of configuration which suggests that hydrogen attacks an adsorbed substrate from the side of catalyst surface.

From this and other results Eshashi hypothesizes the following mechanism (Figure 15). Route 1 leads to retention of configuration and route 2 to inversion.

π-Adsorption of the phenyl group onto the metal surface gives (B) or (B') depending on the type of metal. This is followed by the nucleophilic attack of an electron from the surface of the catalyst on the adsorbed substrate. In the resultant π benzylic complex, there is a tendency toward sp^2 hybridisation at the benzylic carbon, with the C-O bond becoming labile and finally breaking as the oxygen combines with hydrogen from the catalyst surface.

Eshashi's hypothesis is that the stereoselectivity is not determined by the adsorption of the substrate or by the decomposition of (D) and (D') with hydrogen, but by the difference in free energy levels of the two transition states (B) and (B'), since the activation energies for the cleavage of the C-O bond ((B) to (D) and (B') to (D')) is larger than those for the adsorption of the substate ((A) to (B) and (A) to (B')) and decomposition of the carbon-metal bond of the π benzylic complex to the adsorbed products ((D) to (E) and (D') to (E')).

In the case of palladium catalysis the free energy of transition state (B') is lower than that of (B), possibly due to the S_N2 nature of electron attack in route 2 being stereoelectronically advantageous over the S_Ni type of displacement in route 1, in which the leaving group is ejected on the same side as electron attack.

It follows that when nickel is the catalyst, the free energy level of (C) is lower than that of (C'). Nickel has a strong affinity for oxygen, thus it may adsorb the groups containing oxygen more strongly than palladium thereby decreasing the free energy level of (B) and the activation energy involved in the conversion of (B) to (D).[6]

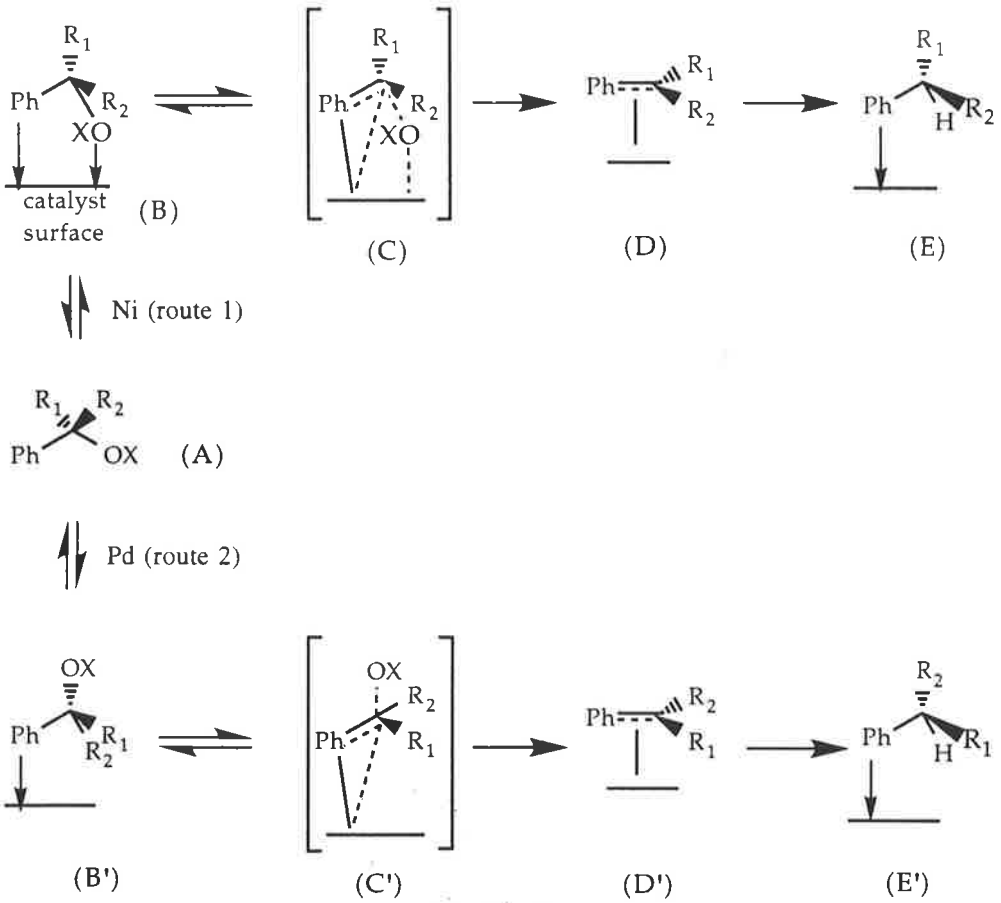
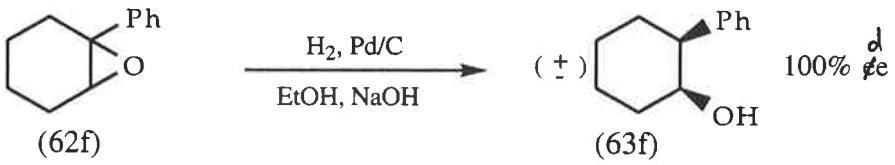


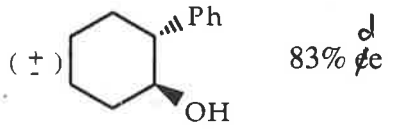
Figure 15

Sugi[42] has hydrogenolysed the epoxide (62f) at room temperature and pressure using a catalytic amount of NaOH. The reaction was competely stereoselective with the use of palladium on carbon to give (63f). The use of Raney nickel gives a poorer d.e. of 83% and with the ~~opposite~~ configuration (63d)* (Scheme 25).



(62f) (63f)

Scheme 25



(63d)

* The letter "d" is used in this thesis to represent a diastereomer.

Analytical Methods[43]

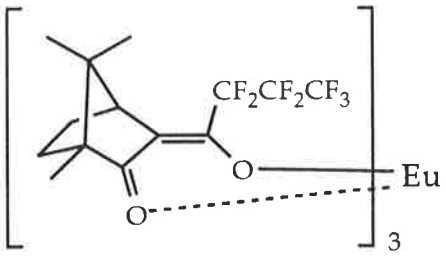
It is necessary to determine the enantiomeric excess of the optically active compounds synthesised with a relatively high degree of accuracy. A number of methods exist for this purpose starting with the classical polarimetry which measures the optical rotation of a compound at a single wavelength. This method has been used since the early 1800s, however it no longer provides the accuracy desired by modern analysts. In any case, it is necessary to know the optical rotation of a ~~compound~~ pure enantiomer before this method can be used to determine the ~~ratios of the enanatiomers~~ e.e.. Without the newer methods of determining e.e. the optical rotation of a compound can only be assumed to be the highest rotation measured. The optical rotation measurement is therefore supplanted by newer methods of determining enantiomeric excess.

For the use of NMR techniques it is necessary to provide a chiral environment to distinguish the magnetic environment of the enantiomers. This has the advantage over optical rotation in allowing the determination of the extent of resolution, reaction rates, degree of asymmetric induction, and optical purity.

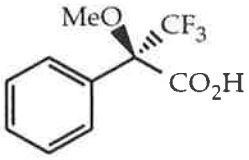
The methods used to cause enantiomers to exhibit diastereomeric differences and hence to be viewed separately are i) a chiral shift reagent, ii) a chiral solvent, or iii) conversion to a diastereomer by covalent σ-bond formation.

The methods i) and iii) are used in this thesis. Tris[3-(heptafluoropropylhydroxy-methylene)-(+)-camphorato] europium(III) derivative (64f) is a commercially available chiral shift reagent (Figure 16). When added to the NMR solution of an optically active compound it causes changes in the ^{1}H NMR spectrum ~~to spread out~~, and ~~the~~ differential diastereomeric interactions usually cause some of the characteristic peaks to separate into two separate peaks, integration of which gives the ratio of the enantiomers and hence the e.e.[43]

Alternatively an alcohol (or amine) can be acylated with Mosher's acid (65f) giving diastereomers. The methoxyl or other resonances of the alcohol portion in the ^{1}H NMR spectrum of the product mixture are often of sufficiently different chemical shift to allow integration. The ^{19}F NMR spectrum can sometimes also be used to view the diastereomeric ratio.



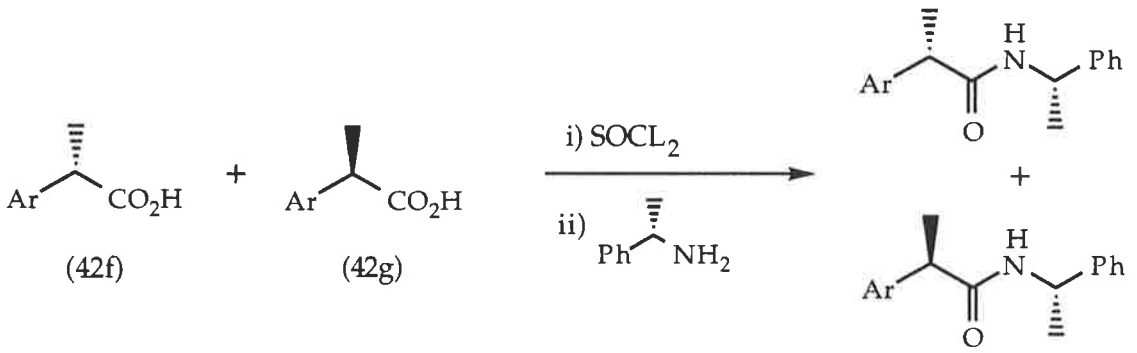
(64f)



(65f)

Figure 16

Liquid chromatography can be used to separate enantiomers when a chiral stationary phase is used to give differential absorption to the enantiomers. Diastereomers (as an enantiomeric mixture derivatised with e.g. (65f)) are separable on an ordinary column. Hayball[44] has developed a suitable method for the determination of optical purity of 2-arylpropanoic acids. A racemic sample of ketoprofen (42r) was converted to the (*S*)-1-phenylethylamides, via the acid chlorides, and it was found that the diastereomers separated by HPLC (Scheme 26). This method was used for the analysis of ibuprofen in the current work.



(42f) (42g)

Ar = 3-benzoylphenyl

Scheme 26

RESULTS AND DISCUSSION

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CHAPTER 1

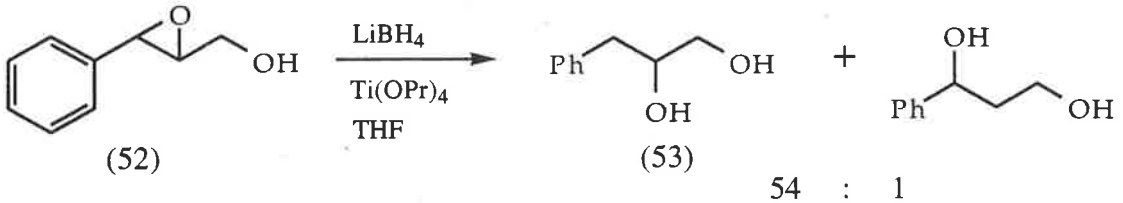
ASYMMETRIC SYNTHESIS OF IBUPROFEN

Ibuprofen is of commercial importance, as it is the most widely used of all the 2-arylpropanoic acid drugs. Although marketed in racemic form, the (*S*) isomer is 160 times more active than the (*R*) enantiomer. Complications can arise in the estimation of dosages because of the (*R*) to (*S*) interconversion which occurs *in vivo*.

The asymmetric synthesis of (*S*)-ibuprofen (1f) was undertaken via an intermediate which can potentially also be used to obtain a variety of *para* substituted arylpropanoic acids in a single synthetic step from this key intermediate. In this case (*S*)-ibuprofen was the only arylpropanoic acid prepared. As outlined in the introduction (p17) this research group has discovered routes to two such key intermediates. The aim was to find a more efficient route than those already discovered in this research group.

Due to the problems encountered in the coupling step of the chloro arene (48) it was decided to try to obtain *p*-bromophenylpropanoic acid (50f) as the key intermediate in the coupling step. This intermediate (50f) could be obtained if a means could be found to reductively cleave the epoxide (25f) regio- and stereoselectively, and also chemoselectively to leave the Br-Ar bond intact (Schemes 13 (p18) and 27). This would form the diol (26f) which would be oxidatively cleaved to give the intermediate sought (50f).

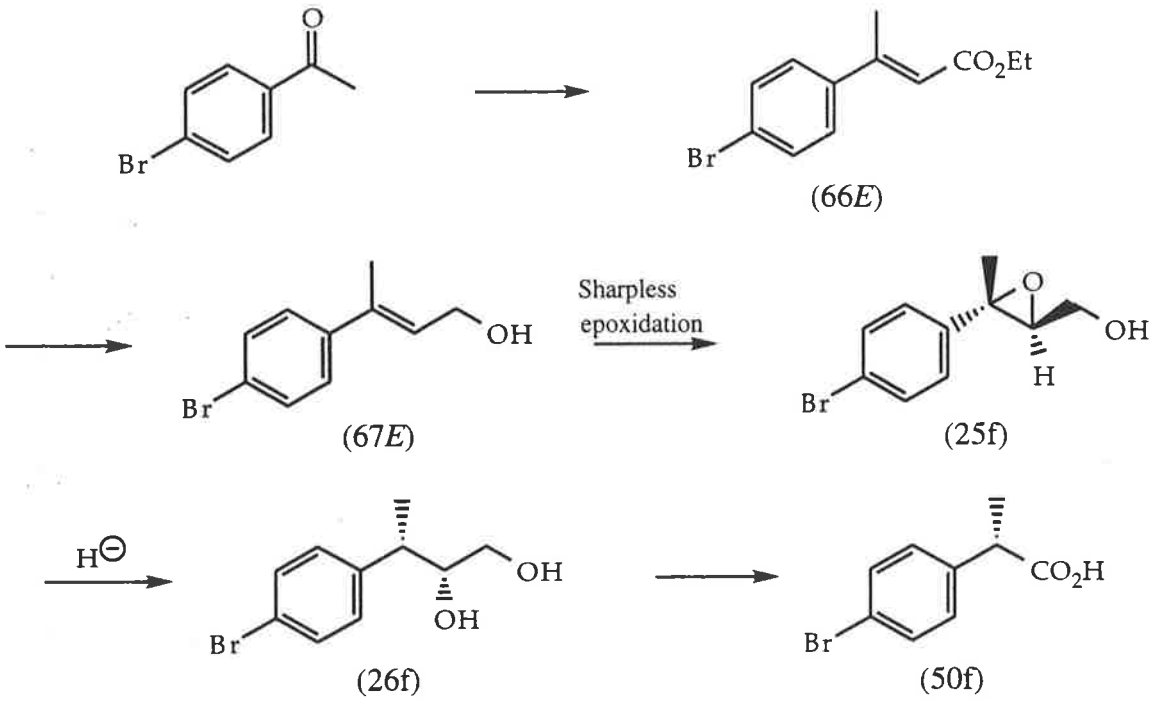
As discussed (p26) Dai has discovered conditions to reductively cleave the epoxide (52) which fulfills the requirement of regioselectivity (Scheme 27). This epoxide (52) of Dai is simpler than the epoxide (25f) in being only secondary at the benzylic centre and as such the regioselectivity is expected to be lower for the trisubstituted epoxide (25f).



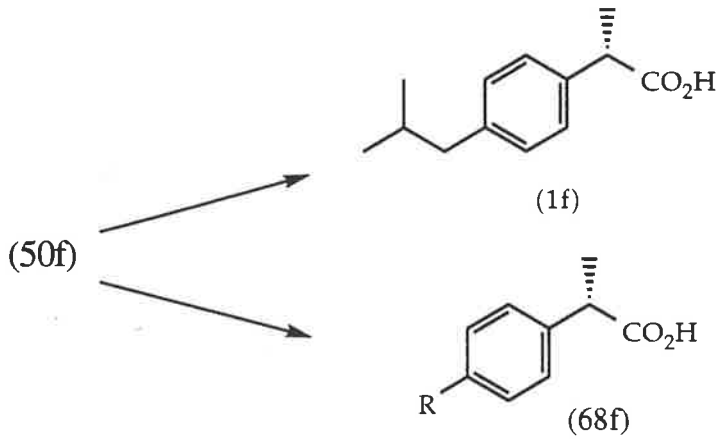
(52) (53) 54 : 1

Scheme 27

The route to be followed (Scheme 28a and 28b) was to form the αβ-unsaturated ester (66*E*) from commercially available *p*-bromoacetophenone by a modified Wittig reaction, this ester would be reduced to the allylic alcohol (67*E*) using lithium aluminium hydride. The Sharpless epoxidation would be used to introduce asymmetry to form the epoxide (25f) and the titanium tetraisopropoxide assisted hydride reduction of Dai would be expected to furnish the diol (26f) after purification of the mixture of regioisomers. Oxidative cleavage of this diol, with ruthenium tetroxide/sodium periodate would give the target key intermediate which would be coupled with the *iso*-butyl group to give ibuprofen (1f) and potentially other arylpropanoic acids (68f).

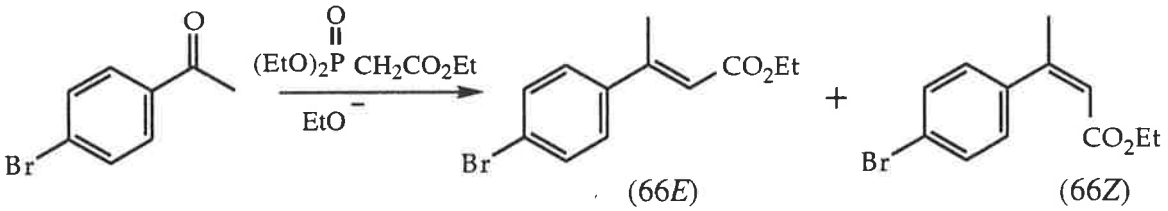


Scheme 28a



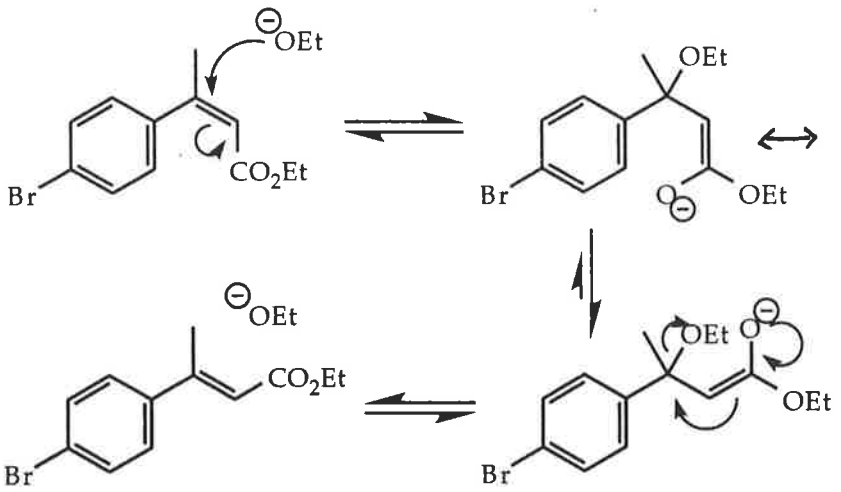
Scheme 28b

A mixture of the esters (66*E*) and (66*Z*) was obtained by the Wittig-Horner[45] reaction via conditions discovered by the author during a preliminary investigation to an earlier piece of work.[46] Thus *p*-bromo-acetophenone reacted with the lithium salt of diethylphosphonoacetate, obtained by use of the base lithium ethoxide in ethanol (Scheme 29). After the reaction was stirred for 42 hours, it was shown by TLC analysis that starting material was still present. Another 0.1 equivalents of phosphonoacetate was added and the reaction stirred another 42 hours. Work-up was achieved by addition of a saturated solution of ammonium chloride and removal of the ethanol solvent under reduced pressure before the precipitated oil was extracted from the now purely aqueous solution with dichloromethane. The ^{1}H NMR spectrum of the crude mixture of esters, obtained in a yield of 99%, indicated a high degree of chemical purity and a diastereomeric ratio of the desired *E* isomer to the *Z* isomer of 30/1. The latter was determined by integration of the distinct signals of the vinylic hydrogens which occur at δ 6.11 and 5.93 respectively. The ^{1}H NMR spectrum of the thermodynamic *E* isomer shows the ethyl resonances to occur as a 3H triplet at δ 1.31 and as a 2H quartet at δ 4.23. The methyl occurs as a singlet at δ 2.54 and the vinylic proton at δ 6.11. The aromatic protons occur as an AA'BB' system at δ 7.31-7.49.



Scheme 29

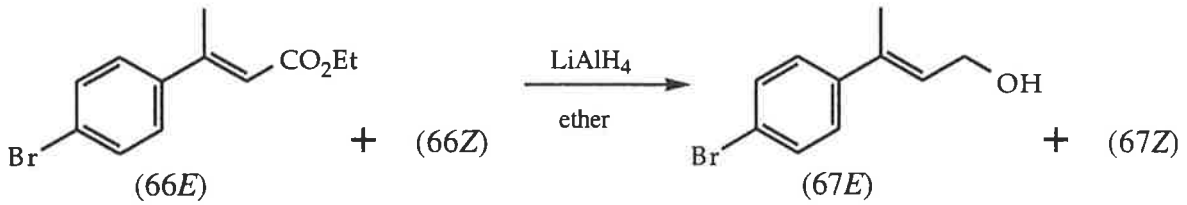
This reaction proceeds initially to give an *E/Z* ratio of only 3/1 but on continued stirring, equilibration gives the observed thermodynamic ratio. This equilibration was followed by TLC and the final ratio determined by ^{1}H NMR spectroscopic analysis. A proposed mechanism for this equilibration involves addition of ethoxide to the activated carbon-carbon double bond, rotation around the remaining single bond and elimination to return the αβ-unsaturated ester in the thermodynamically controlled ratio of 30/1 (Scheme 30).



Scheme 30

Use of another base such as potassium *tert*-butoxide[47] leads to the kinetic ratio of only 3/1 most likely for the reason that addition of the bulky *tert*-butoxide ion to the double bond does not occur.

Use of sodium ethoxide leads to a slightly lower ratio than that observed for lithium ethoxide.



Scheme 31

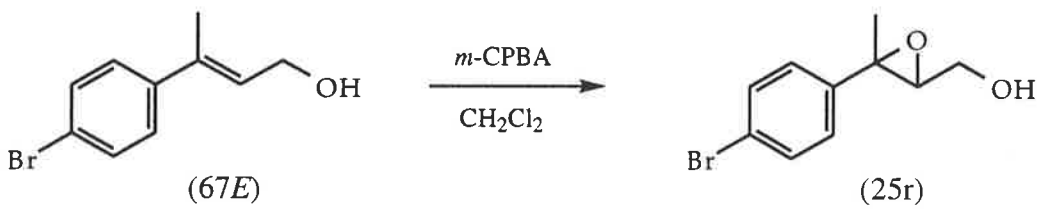
Reduction of this crude mixture with lithium aluminium hydride at -78°C gave the mixture of allylic alcohols (67*E*) and (67*Z*) as an off-white solid (Scheme 31) which was sublimed at 100-110°C/0.1 T to give the pure alcohols in an overall yield of ~~of~~ 83% based on starting acetophenone. This reaction is performed at low temperature to prevent 1,4-conjugate addition to the double bond[6] of the αβ-unsaturated esters and further reduction of the double bond in the product allylic alcohols. The *E* isomer was taken to diastereomeric purity by 3 recrystallizations from ether/hexane(the solution ~~being~~ was cooled to -15°C each time) but this decreased the yield to 41% (again based on acetophenone), ~~but~~ however, pure (67*E*) was obtained as white needle-like crystals of melting point 58-59°C. The ^{1}H NMR spectrum of the purified

allylic alcohol (67*E*) shows the hydroxy proton as a singlet at δ 1.79, the methylene protons occur at δ 4.34 as a doublet coupled to the triplet vinylic proton at 5.95 ppm. The latter shows further fine coupling to the methyl which resonates as an apparent singlet at δ 2.04 and the aromatic hydrogens again appear at 7.24-7.44 as an AA'BB' system.

The diastereomeric purity in the chloro series (intro. p22) was increased by recrystallization at the epoxide stage, as the chloro allylic alcohols are oils. One recrystallization of the chloro epoxide (46) was sufficient to give diastereo and enantiomeric purity as shown by ^{1}H NMR spectroscopic analysis. It is likely that this would also be a better stage at which to purify in the bromo series but it was never attempted. It is known that optically active epoxy-alcohols are purified very efficiently by recrystallization.[26]

The next step in the synthetic sequence was the Sharpless epoxidation. However, initially the formation of the racemic epoxy alcohol (25r) was investigated as this would provide easier access to the epoxide to allow investigation of the subsequent steps leading to ibuprofen, as well as to provide a racemic sample which would be required for analysis of the optical purity of the epoxide obtained after the Sharpless procedure.

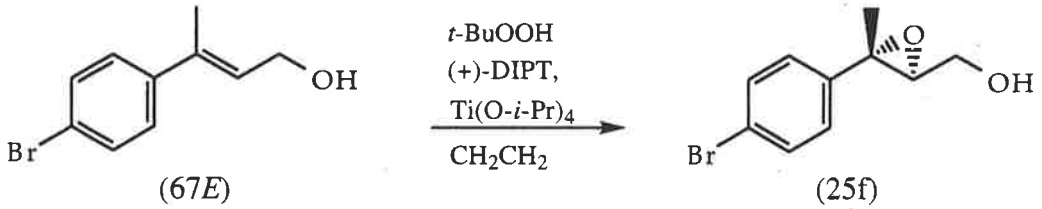
Thus a solution of the allylic alcohol (67*E*) in dichloromethane was treated with one equivalent of *m*-chloroperoxybenzoic acid.[48] After three hours at room temperture the reaction was worked up by reduction of excess oxidizing agent to give the racemic epoxide (25r) in 94% yield which was recrystallized from ether/hexane to give the pure epoxide in a yield of 66% (Scheme 32). ^{1}H NMR spectroscopy shows the hydroxy proton to occur as a broad singlet at δ 1.76; the methyl resonates as a singlet at δ 1.68. The diastereotopic methylene protons occur as two double doublets at δ 3.84 and δ 3.96 coupled to each other and to the methine proton at δ 3.05. The aromatic hydrogens occur at δ 7.19-7.49 as an AA'BB'system.



(67*E*) (25r)

Scheme 32

Asymmetry was introduced with the Sharpless epoxidation reaction[26] with the pure allylic alcohol (67*E*) as substrate. As the synthetic target was the *S* isomer of ibuprofen and it is known that the reduction of the epoxide will occur with inversion of configuration, it is seen that the *S* configuration is desired at the benzylic position (allowing for change in group priority) of the epoxide. The rules of Sharpless (p23) show that the L-(+)-tartrate should be used to obtain this isomer. Thus a dichloromethane solution of allylic alcohol (67*E*) was treated with an excess of *tert*-butylhydroperoxide and a catalytic amount of titanium tetraisopropoxide and diisopropyl ester L-(+)-tartrate (Scheme 33) to give the epoxide (25f) as an off-white solid. The epoxide was removed from polar impurities in the crude mixture by sublimation at 125°C/0.02 T and recrystallized from dichloromethane/ether to give the epoxide (25f) in 57% yield, which was shown to be pure by ^{1}H NMR spectroscopy. The crystals were white, needle shaped but had an unusually wide melting range of 124-131°C. The optical rotation was $[\alpha]^{20}_D$= 26.52° (c= 1.32, ethanol).

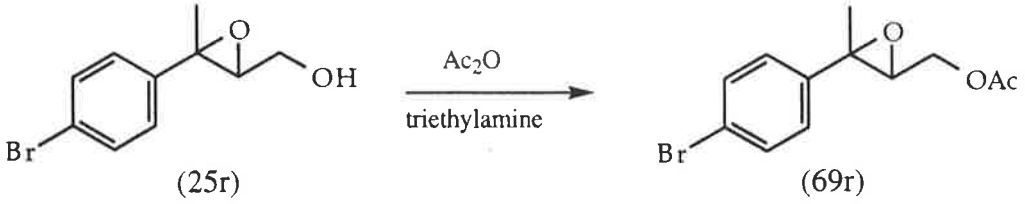


(67*E*) (25f)

Scheme 33

Past experience in this group has shown that the optical purity of these epoxy alcohols is most effectively determined as the acetate derivative, by 300 MHz ^{1}H NMR spectroscopy with the chiral shift reagent Eu(hfc)$_3$. The (epoxy alcohol)-(shift reagent) complex is otherwise too tightly bound and gives rise to excessive line broadening, preventing satisfactory separation of peaks due to diastereomeric interaction of the enantiomers.

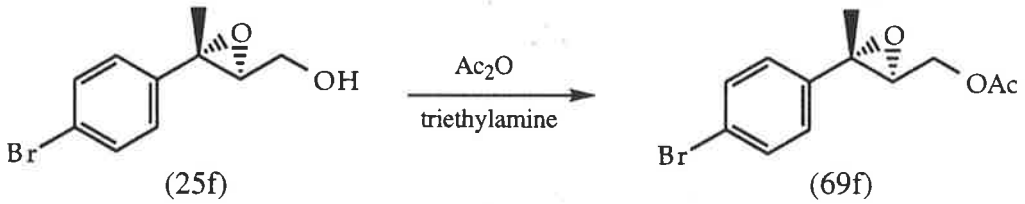
Thus the racemic epoxide (25r) was acetylated in triethylamine as solvent with the reagent acetic anhydride to give the acetylated product (69r) (Scheme 34). The ^{1}H NMR spectrum of the acetate (69r) is similar to that of the epoxide with an additional singlet methyl peak at δ 2.11 and the absence of the OH peak.



Scheme 34

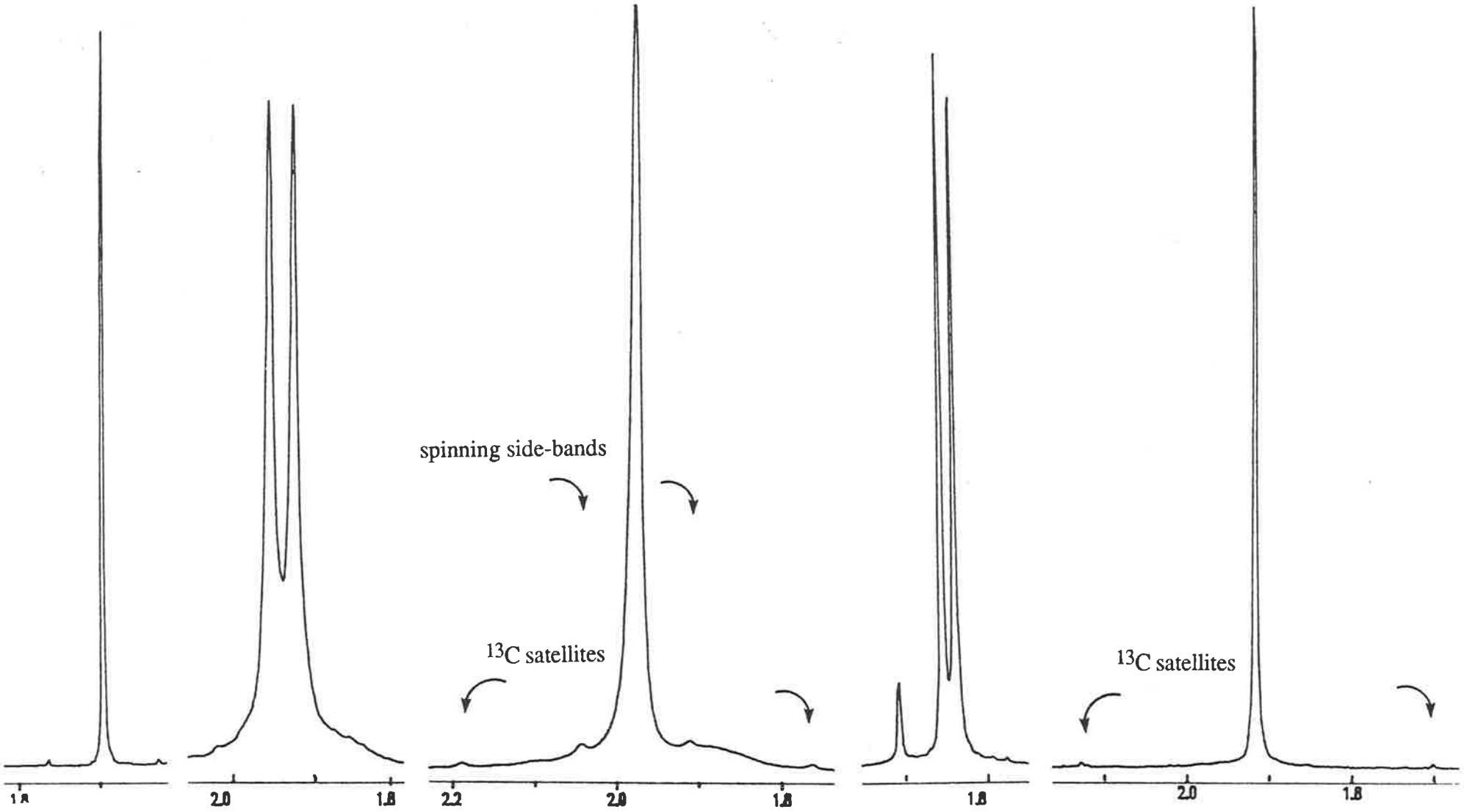
The ^1H NMR spectrum of a d-chloroform solution of the racemic acetate (69r) and a (mass) equivalent of $Eu(hfc)_3$ showed the characteristic downfield shift but with some line broadening (Figure 17b). Each peak was now also twinned–the signals of the enantiomeric groups are no longer degenerate. The signal for the methyl group attached directly to the stereogenic centre was the most diagnostic, however the separation of the peaks was not baseline. The average of the chemical shift of the methyl groups of the enantiomers had shifted from δ 1.69, in the non-chiral environment, to δ 1.92 now with a separation of 0.030 ppm.

It was found that addition of 0.25 mole equivalent of water and dilution with d-chloroform caused the resolution to be greatly enhanced with only a small loss of shift. The methyl peaks now resonated more upfield at δ 1.83 and the separation had decreased to 0.016 ppm, however the separation was closer to baseline (Figure 17d).



Scheme 35

Similarly the optically active epoxide (25f) was acetylated (Scheme 35) and the ^1H NMR spectrum, in particular the methyl signal, was observed after addition of i) chiral shift reagent (Figure 17c), ii) water and iii) further dilution with d-chloroform (Figure 17e). After such treatment only a single very well resolved methyl peak was observed which now resonated at δ 1.89 (Figure 17e). Given the smooth baseline, it was assumed that even 1% of the other enantiomer would be apparent, thus optical purity of 98%+ was confidently claimed. The next largest peaks from the main signal were the symmetrically disposed ^{13}C satellites which each equal 0.5% of the main peak in area.



a) in the absence of shift reagent

b) racemic material with CSR

c) optically active material with CSR

d) racemic material with CSR and water

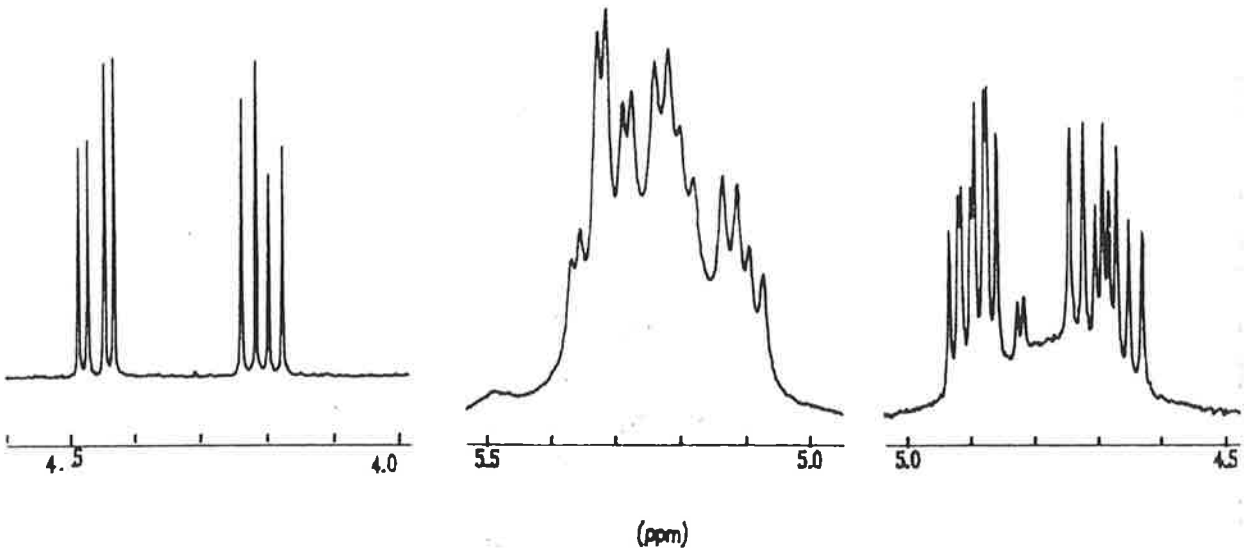
e) optically active material with CSR and water

CSR = chiral shift reagent

Figure 17

The improvement in resolution on the addition of a small amount of water, is best seen with the methylene signals and this is diagrammed in (Figure 18) for (69r) which shows a) the non-shifted signal, b) the chiral shifted signal, and c) the chiral shifted signal, with water and additional d-chloroform added.

Possible reasons for the resolution enhancement is the altering of the configuration of the epoxide/europium complex when it forms in the dynamic equilibrium between the complexed and uncomplexed states or a more rapid rate of exchange between these states.



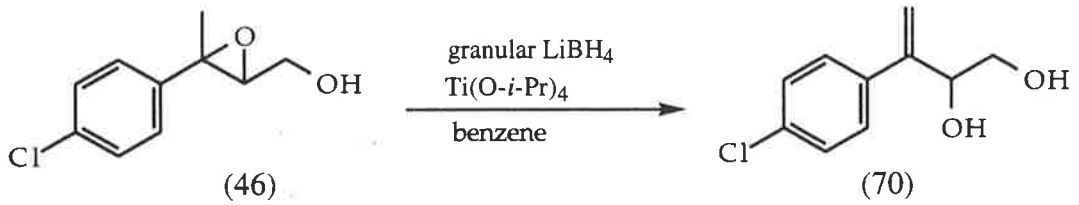
a) no shift reagent b) shift reagent c) shift reagent + water

Figure 18

It was now necessary to reductively cleave the epoxide (25f) to obtain the diol (26f) as ~~fully~~ selectively as possible. As noted, the regioselectivity was by-and-large expected to be the sole cause of problems in this transformation. The epoxide (25f) from which it was desired to obtain the diol differs from the model compounds of Dai[32] in being more sterically hindered– tertiary at the reaction center and by the bulk of the aryl group. The bromo group would be expected to stabilize the intermediate carbocation through resonance, but its influence on the reaction, otherwise, was not known.

The corresponding chloro epoxy alcohol (46f) was used for trial reactions as it was immediately available. This epoxide was reacted with a solution of titanium tetraisopropoxide

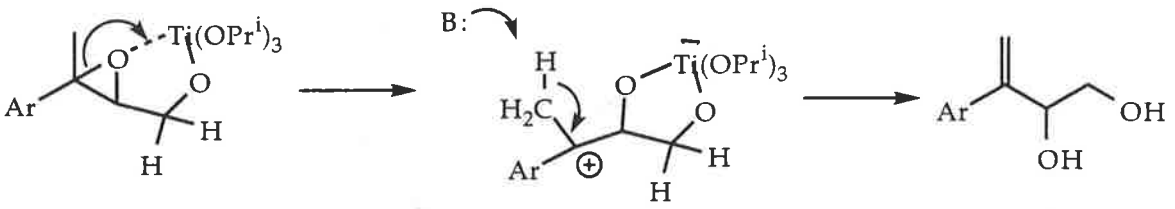
in benzene for 10 minutes before a suspension of lithium borohydride in benzene was added and the heterogeneous mixture stirred at room temperature for 18 hr (Scheme 36). Work-up was achieved with a 5% solution of sulphuric acid and resulted in the purely rearranged product (70); no reduction was evident as seen by ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum showed two broad singlets due to the OH groups at δ 2.74 and 3.18, the diastereotopic methylene protons occur as double doublets at δ 3.43 and 3.65 coupled to each other and the double doublet methine proton which occurs at δ 4.73. One vinylic proton resonates at δ 5.40 as a singlet and the other resonates at δ 5.45 as a fine triplet with coupling from undetermined protons. The aromatic protons resonate as an AA'BB' system at δ 7.26-7.31. The IR spectrum shows absorbtion at 1630 cm^{-1} due to the alkene.



(46) (70)

Scheme 36

It was found that the same rearrangement occurs when the reaction was carried out in the absence of the reducing agent. The epoxide was stirred for 15 h at room temperature with 2 equivalents of titanium tetraisopropoxide in benzene and the product of this reaction, after recrystallization, was the diol (70) obtained as white flakey crystals of melting point 72-74°C in a yield of 76%. A similar rearrangement to this has been observed by Sharpless.[49] The likely mechanism is shown in Scheme 37.

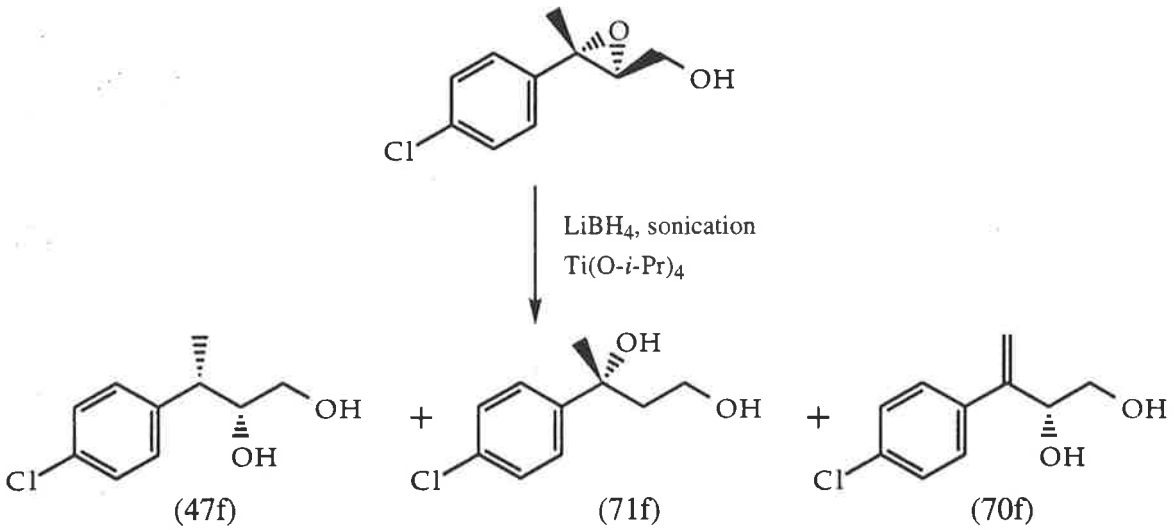


(70)

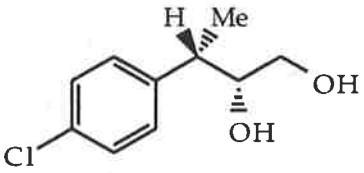
Ar = 4-chlorophenyl

Scheme 37

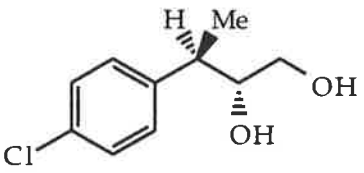
As reduction had not occurred, it was considered likely that the borohydride had remained in the undissolved state. A possible means to solve this problem was to use sonication, which produces a fine suspension and hence a greater surface area and rate of dissolution. Thus a previously sonicated mixture of the borohydride in THF was added to a THF solution of the epoxide-titanium complex. The reaction was run at 0°C over 24 h and resulted in the formation of a mixture of the regioisomers (47f) and (71f), and the diol (70f), as shown by the ^{1}H NMR spectrum of the crude isolated mixture (Scheme 38). The presence of only the single 1,2-diol diastereomer (47f) was indicated in the ^{1}H NMR spectrum, which suggests that the reduction was stereoselective with inversion. However this is not certain as the isomer which is obtained from reductive cleavage of the benzylic epoxide bond with retention of configuration has not been obtained pure and hence its ^{1}H NMR spectrum is not known. This isomer is the diastereomer (47d)* (Figure 18) and is expected to have a different spectrum from that of the diol (47f), and reasonable evidence for which will be presented on page 52.



Scheme 38



(47f) results from inversion



(47d) results from retention

Figure 18

* The letter "d" is used in this thesis to represent a diastereomer of a compound.

When the reaction was performed with continuous sonication poor regioselectivity for the 1,2-diol (47) was observed and only 50% of the epoxide was consumed. It was found to be sufficient to add the borohydride in the solid form directly to the dissolved titanium-epoxide complex followed by a few minutes of sonication and to subsequently stir the reaction mixture vigorously.

Different solvents were tried, to determine conditions which minimized formation of the eliminated product (70) and gave the highest regioselectivity for the 1,2-diol (47f) (Table 2). Reactions were performed on approximately 70 mg of epoxy alcohol (46), used 2 equivalents of titanium tetraisopropoxide and 8 equivalents of lithium borohydride, except for the reduction reactions which used toluene and xylene as solvents, where greater than 8 equivalents were used.

It was later found that the number of molar equivalents of borohydride effects the regioselectivity greatly, and use of less than 8 equivalents results in a greater proportion of the undesired 1,3-diol as well as a greatly reduced rate. Use of only 3 equivalents of borohydride did not give any reduction at all, mainly starting epoxide and a small amount of rearranged product was recovered. This necessity to have at least 8 equivalents of borohydride has also been noticed by Lau[50] in the $ZnI_2/NaCNBH_3$ reducing system described in the referenced paper. It is therefore likely that the greater proportion of 1,2-diol formed by use of toluene and xylene as reaction solvents is also due to the extra equivalents of borohydride. A reaction to confirm this, which uses only 8 equivalents of borohydride was, however, not done.

The work-up conditions involved the addition of water and filtration of the precipitated titanium salts through a pad of celite and then extraction with dichloromethane. It was eventually discovered that addition of concentrated HCl to the aqueous phase and precipitated titanium salts, that had been extracted to exhaustion, liberated an additional *ca.* 27% (on top of 70% recovered from the non-acidic work-up) in a particular reaction that had been carried out on a larger scale (400 mg Br epoxide). The ^1H NMR spectrum of this additional extraction of the acidified solution showed that it was mostly composed of the 1,2-diol (47) as well as larger amounts of the alkene diol (70). The 1,3-diol (71) formed only a small proportion. This clearly shows that the titanium salts had been not fully hydrolysed and that the two 1,2-diols

had a greater affinity to co-ordination with titanium. Thus the percentages of products listed below (Table 2) represents the ratio of diols in the recovered mixture, not the actual ratio of diols that the reaction produced. The latter ratio is more closely represented for the last two entries (epoxide (25f)).

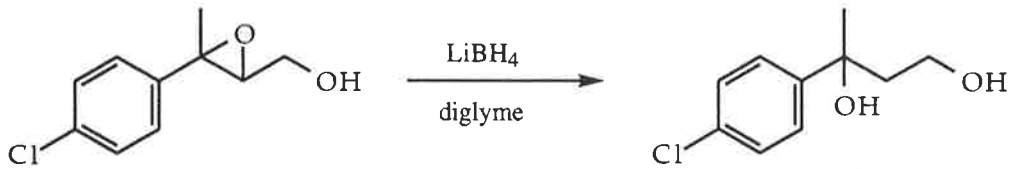
Dai used 5% sulphuric acid to hydrolyse the titanium salts in work-up, however, it was initially considered that the presence of acid may cause degradation of the product diols and possible remaining starting epoxide (46), so water was used in the work-up. This did not however appear to be the case.

epoxide	solvent	no. equiv. $LiBH_4$	1,2-diol %	1,3-diol %	alkene diol %
(46)	THF	6	28	66	6
(46)	ethyl ether	8	55	39	6
(46)	butyl ether	8	34	61	5
(46)	nitrobenzene	8	41	25	34
(46)	benzene	8	56	36	8
(46)	toluene/5°C	16	73	19	8
(46)	toluene/15°C	16	72	21	8
(46)	xylene	16	76	21	3
(46)	toluene	3	0	0	some
(25f)	X=Br xylene	16	77	19	4
(25f)	X=Br xylene	12	80	16	4

Table 2

The last row gives the optimum conditions found for reductive cleavage of the bromo epoxide (25f).

A reduction reaction performed in the absence of titanium tetraisopropoxide gave the 1,3-diol (71) as the sole product (Scheme 39) as seen by the ^{1}H NMR spectrum of the crude product material . This shows the resonance of the methyl to occur as a singlet at δ 1.51. The resonances of the diastereotopic hydrogens of the methylene group closest to the stereogenic centre occur as double double doublets at δ 1.94 and 2.05, and the resonances of the group further from the stereogenic centre occur as multiplets at δ 3.50 and 3.71. The hydroxyl protons resonate at δ 3.40 and 4.40 as broad singlets and the aromatic protons resonate between 7.26-7.36 as an AA'BB' system.



(46) (71)

Scheme 39

Due to the expense of lithium borohyride the reduction was attempted with use of sodium borohydride which Dai found gave good regioselectivity but slow reaction rate due to its low solubility, however no reduction was effected for the epoxy alcohol (46).

A section of an ^{1}H NMR spectrum of a crude deuterium exchanged reaction mixture is shown in Figure 19. Distinct signals due to each of the three diols can be identified and integration of these signals gave the percentages listed in Table 2.

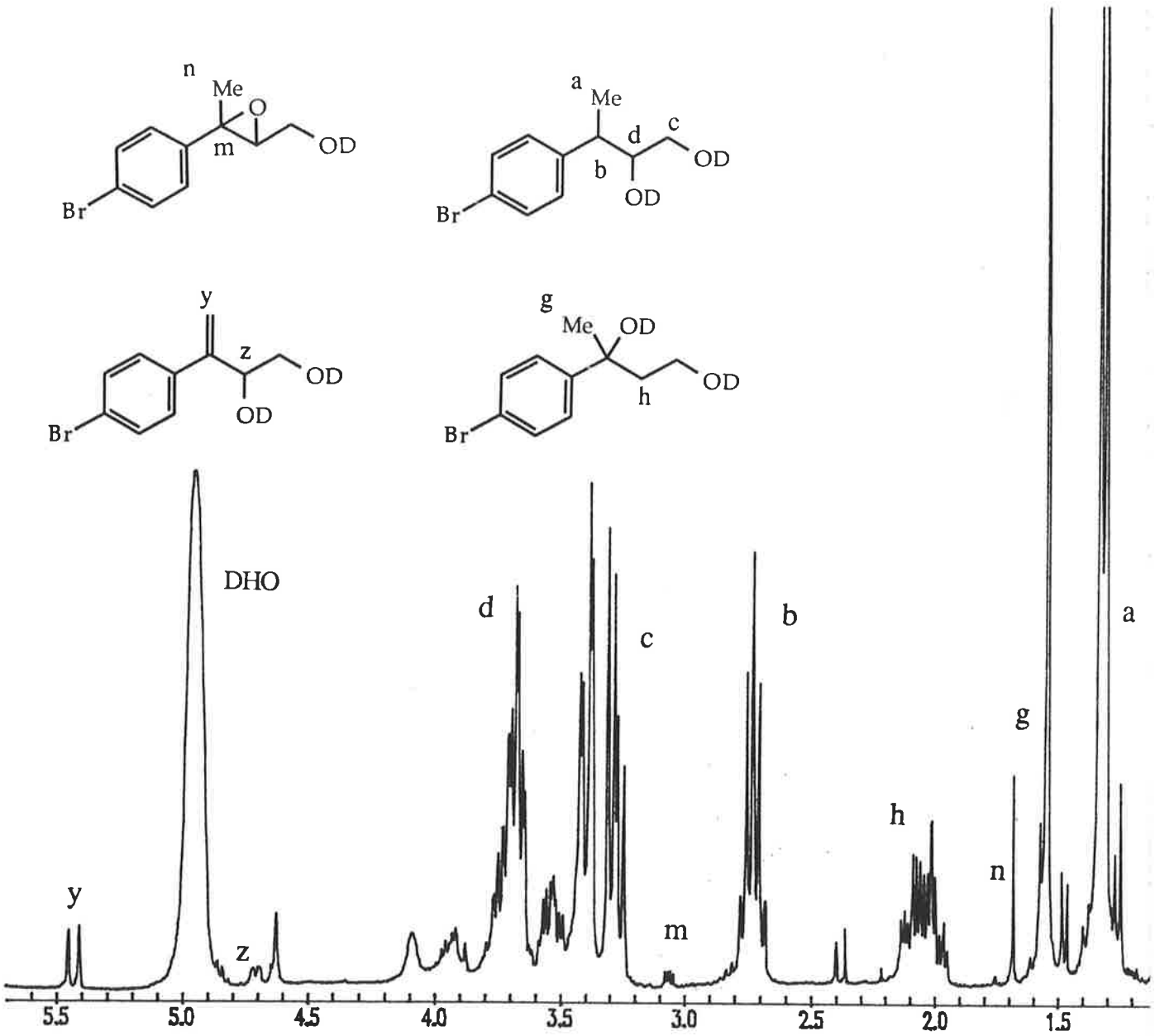
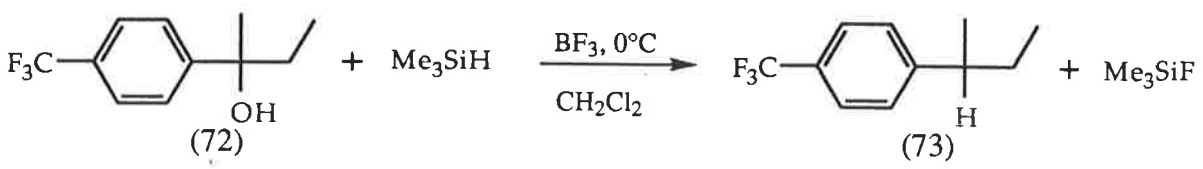


Figure 19

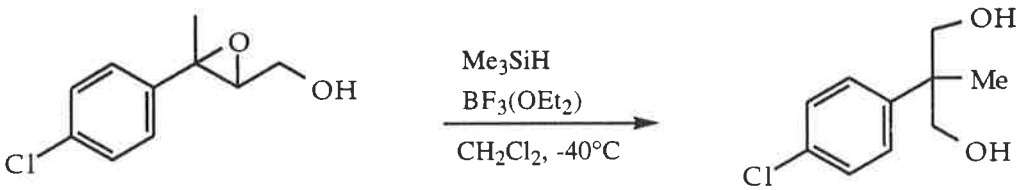
Several other possible methods of reductive cleavage of benzylic C–O bonds were attempted, some of which are described below.

Fry[51] describes the reducing system of organosilane/boron trifluoride used to reduce benzylic alcohols (Scheme 40). The benzylic alcohol (72) is reduced to the hydrocarbon (73) via the carbocation.



Scheme 40

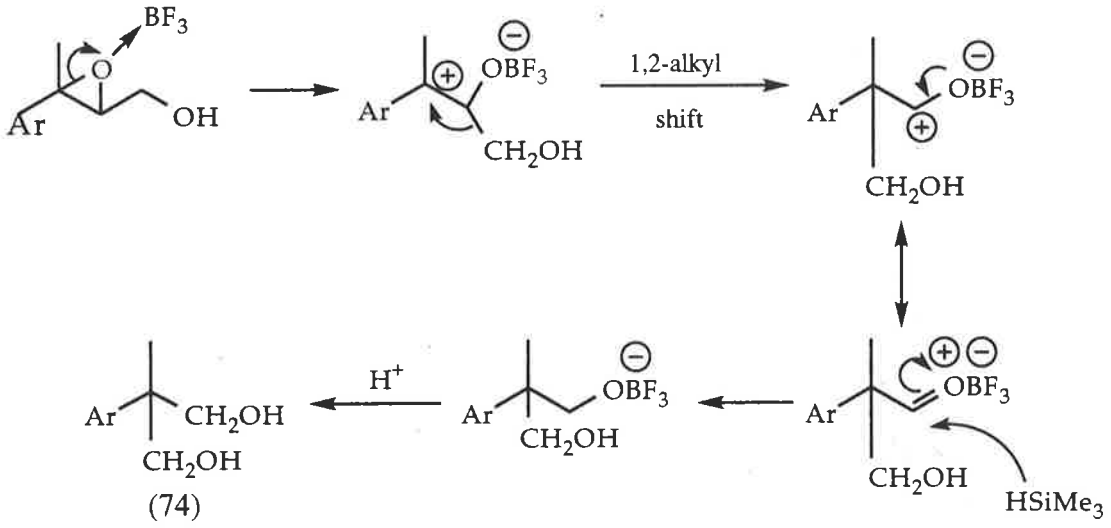
It was hoped that the use of boron trifluoride etherate, a weaker Lewis acid, would weaken the benzylic C-O bond sufficiently to allow reduction by an S_N2 process to take place, without breaking the bond completely (as in S_N1 above) which would cause racemisation and possibly give rearrangement. However, this and a reaction temperature of -40°C were not sufficiently mild to cause the specific reaction, rather rearrangement followed by reduction gave the diol (74) in an isolated yield of 38% after chromatography and recrystallization (Scheme 41).



(46) (74)

Scheme 41

The ^1H NMR spectrum of the pure diol (74) is interestingly simple as the ~~methanol~~ hydroxymethylene groups are enantiotopic. The methylene hydrogens are diastereotopic and resonate as a 4H AB quartet at δ 3.84, the two hydroxy hydrogens occur as a 2H singlet at δ 2.43. The methyl peak occurs at δ 1.24 and the aromatic hydrogens resonate as a narrow AA'BB' system at δ 7.34. A possible mechanism to account for this rearrangement is shown below (Scheme 42). The reason that an alkyl shift occurs instead of the usually more favourable hydride shift is not known.



(74)

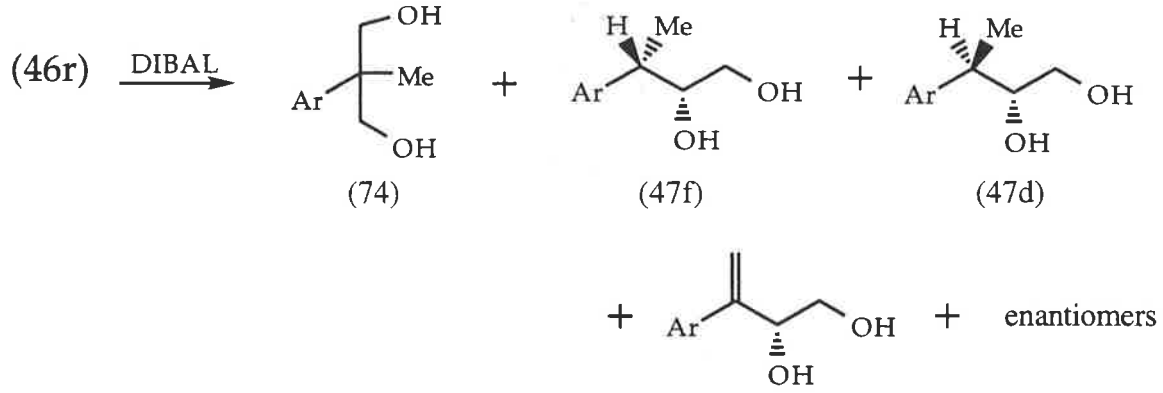
Scheme 42

Kishi[52] claims that DIBAL reduction in benzene at room temperature of certain 2,3-epoxy alcohols proceeds regio- and stereoselectively. A mechanistic explanation of this involves initial complexation of aluminium cation with the alcoholic group. Aluminium cation serves as a Lewis acid which facilitates intermolecular hydride reduction.

The epoxide (46) was reacted with DIBAL according to the conditions reported by Kishi (Scheme 43) and the crude product mixture analysed by ^{1}H NMR spectroscopy. This showed that the rearranged/reduced diol (74) was the major product, the formation of which was most likely catalysed by the strongly Lewis acidic aluminium cation.

Resonances due to the diol (47f), the ^{1}H NMR spectrum of which is known (p22), were present–a quintet at δ 2.73 due to the benzylic proton and a doublet signal at δ 1.32 due to the methyl group. Adjacent to each of these signals was a resonance of the same type and of similar height–a quintet which occurs at δ 2.80 and a doublet which occurs at δ 1.26. These signals were assigned to the diastereomer (47d). If this analysis is correct then the reduction is seen to be non-stereoselective as it was for the reported reactions of Kishi.

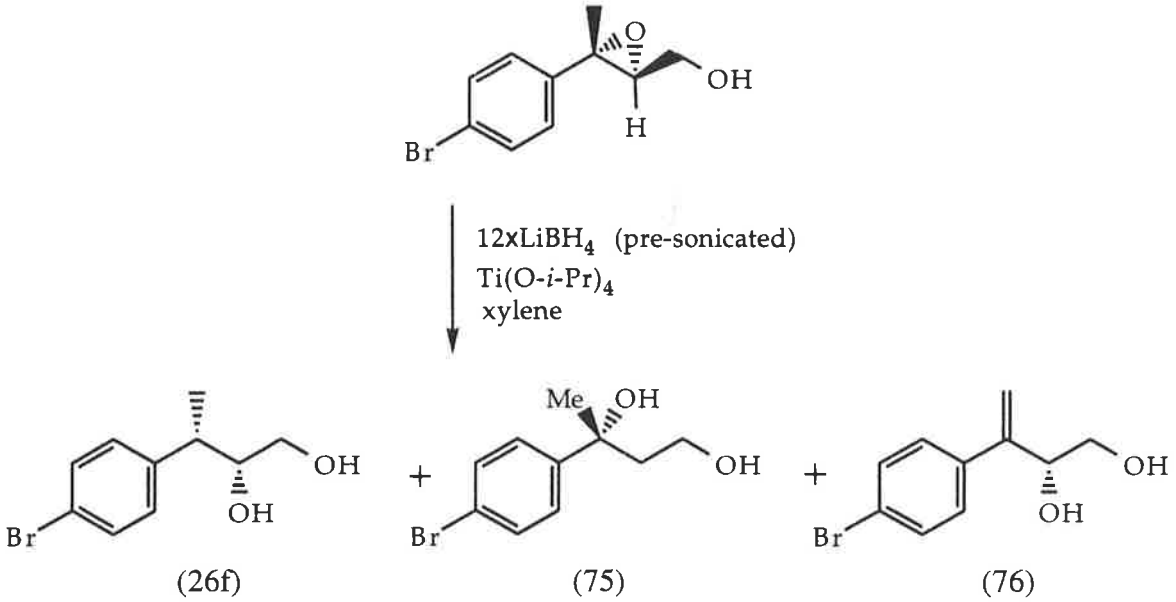
The 1,3-diol (71) was not present, which shows that the reduction was regioselective. The rearranged alkene diol (70) was present in small amount.



Ar = *p*-chlorophenyl

Scheme 43

In continuation from page 49 the reaction conditions which give the optimal yield of the bromo diol (26f) are shown below (Scheme 44).



(26f) (75) (76)

ratio (26f)/(75)/(76)= 80/16/4

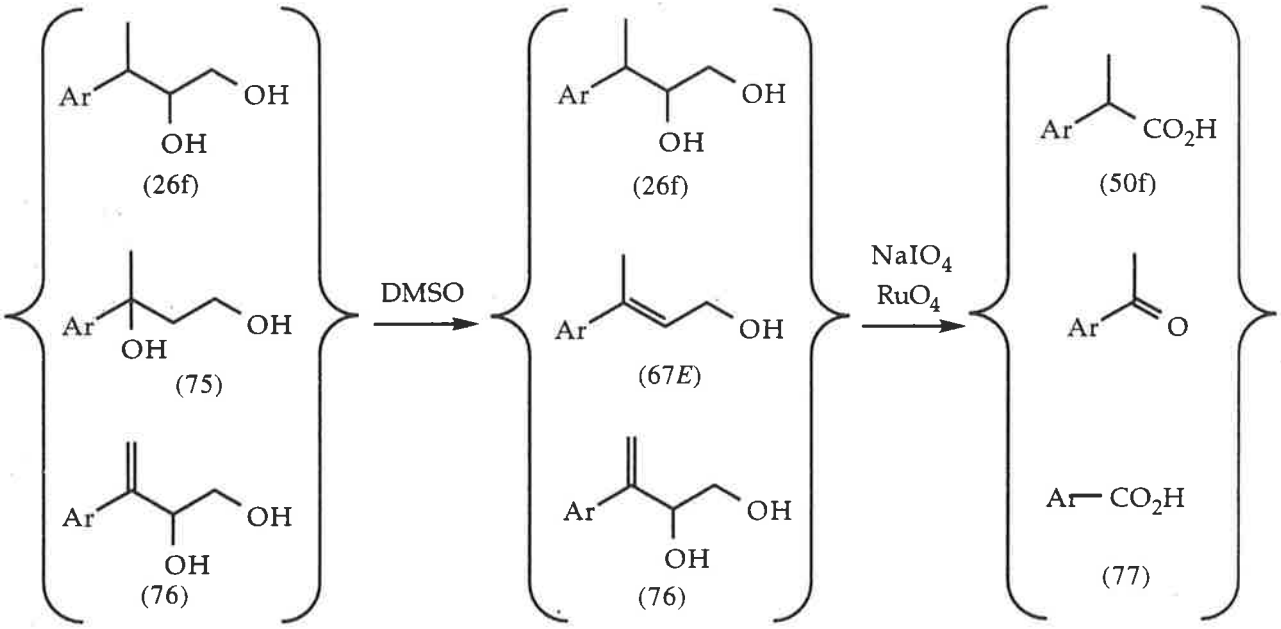
Scheme 44

an attempt was made to separate

The mixture of diols, obtained from reduction of the bromo epoxide (25f) with lithium borohydride and titanium tetraisopropoxide in the solvent xylene, ~~was attempted to separated by chromatography~~, however the 1,2-diols (26f) and (76) ~~were~~ eluted simultaneously and the Rf of the 1,3-diol (75) was very close to that of these two compounds. It was therefore decided to try to find a chemical method of separation which would be less time consuming and also less expensive and so could be applied more easily to larger quantities.

It is known[53] that dimethyl sulphoxide dehydrates *tert*-aliphatic and *tert*-benzylic alcohols in the presence of secondary alcohols when heated at 160-185°C for 9-16 hours.

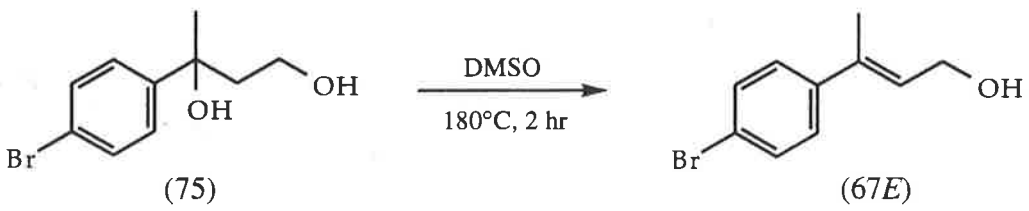
Thus the mixture of alcohols, when placed under these conditions would be expected to dehydrate the 1,3-diol (75) selectively to the alcohol (67*E*) and leave the other two alcohols (26f) and (76) untouched (Scheme 45). Subsequently, conditions of oxidative cleavage which use ruthenium tetroxide would be expected to oxidize the 1,2-diol (26f) to the desired acid (50f), the allylic alcohol (67*E*) to *p*-bromoacetophenone and the alkene diol (76) to the benzoic acid (77). The neutral bromoacetophenone could then be washed out of a basic aqueous solution of the three compounds with dichloromethane, to leave the two acids (50f) and (77). These could be separated either by recrystallization or on the basis of differential acid strength, to give the key intermediate acid (50f) as the sole compound.



Ar = *p*-bromophenyl

Scheme 45

Thus conditions were found that completely dehydrate the 1,3-diol (75) to the allylic alcohol (67*E*). This was found to be 2 hours at 180°C as seen by TLC (Scheme 46).



Scheme 46

The mixture of diols was allowed to react under these conditions, and the reaction monitored by TLC which showed the disappearance of 1,3-diol. DMSO was distilled off under high vacuum, however the distillation was discontinued before all DMSO was removed, approximately 1 ml remained. This was a mistake and caused problems in the later purification steps. These non-optimized conditions are reported however as the reactions which take the mixture of diols to the bromo propanoic acid (50f) were only performed twice and these were the best conditions obtained.

This mixture was placed under the oxidative conditions of Sharpless.[54] Use of ruthenuim tetroxide catalyst, and the co-oxidant sodium periodate in the solvent system of carbon tetrachloride, acetonitrile and water gave a product mixture that was manipulated in the following manner: the residue was placed under reflux in sodium bicarbonate solution for 10 minutes to ionise the acids. After cooling, the solution was washed with dichloromethane, and the washings concentrated . The ^{1}H NMR spectrum of this residue shows the presence of *p*-bromoacetophenone,[55] and a strong peak present at δ 2.98 was found to be due to methyl sulphone.[56] This was formed by oxidation of the dimethyl sulphoxide that was not completely removed from the last step. A small amount of unidentified material was also present.

The remaining bicarbonate solution was acidified and extracted with dichloromethane and the extractions concentrated. The ^{1}H NMR spectrum of the residue showed that the two expected acids were present, the methyl of the desired acid (50f) resonates as a doublet at δ 1.50, the benzylic methine proton occurs as a quartet at δ 3.71 and the 4H AA'BB' system occurs between δ 7.19-7.47. The aromatic hydrogens of *p*-bromobenzoic acid[57] (77) resonated as an AA'BB' system between δ 7.59-7.94. Apart from methyl sulphone which was present again, the rest of the spectrum was clean.

It was found that a dichloromethane solution of the two acids (50f) and (77) could be separated by addition of finely ground solid sodium bicarbonate and to stir this heterogeneous mixture for 2 days. *p*-Bromobenzoic acid (77) reacts preferentially with bicarbonate to leave the arylpropanoic acid (50f) in solution. The salt was filtered off and the organic material collected by acidification and extraction to give a mixture of the benzoic acid (77) and the

propanoic acid (50f) which were present in approximately equimolar amounts. The filtrate contained only aryl propanoic acid (50f). A yield of approximately 70% of the propanoic acid (50f) was obtained in a particular trial reaction.

The pK_a of *p*-bromobenzoic acid (77) is 3.99[58] and that of *p*-bromophenylacetic acid is 4.19[58] (that of the propanoic acid (50) could not be found) which is equivalent to an acidity difference of these acids of $10^{4.19-3.99}$= 1.58. This appears to be sufficient to allow separation on the basis described.

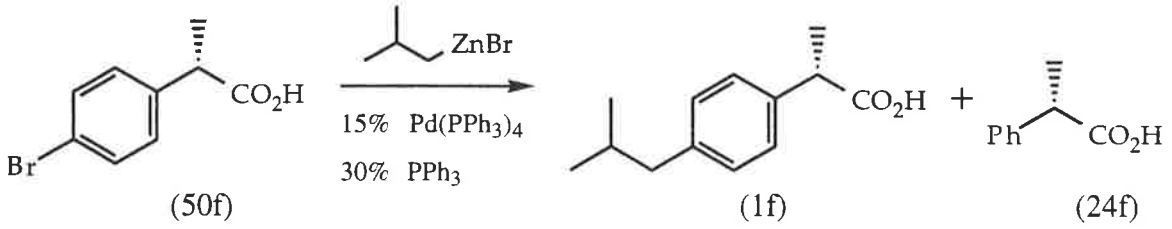
Problems were experienced due to the presence of methyl sulphone which occurred in both the organic and aqueous phases and for this reason accurate yields were not obtained. The crude (*S*)-*p*-bromoarylpropanoic acid (50f) obtained in this way was recrystallized from water. Methyl sulphone, which floated on the hot recrystallizing solution, was removed at this stage . The purified acid (50f) was obtained in a yield of 17% based on the epoxide (25f). The ^{1}H NMR spectrum of this purified sample showed a high degree of purity, the doublet methyl occurs at δ 1.18, the quartet benzylic proton at δ 3.69 and the multiplet aromatic protons between δ 7.17-7.48. The melting point was 104-106°C and the optical rotation $[\alpha]_D^{20}$= 49°1' (c= 1.01, ethanol).

No attempt was made to optimize these reaction and purification steps, as it was clear that the inefficiency of the epoxide opening, particularly the large number of equivalents of lithium borohydride (which is an expensive reagent) needed to effect the reduction would make this reaction sequence unattractive.

Various side chains could potentially be coupled to this intermediate (50f) to give a wide range of optically active aryl propanoic acids in just one step, however the coupling reaction was only performed with the *iso*-butyl group to give (*S*)-ibuprofen.

The reagent, zinc *iso*-butyl bromide was prepared from the corresponding Grignard reagent and zinc chloride.[59] The catalyst tetrakis(triphenylphosphine)palladium(0) and 2 equivalents (relative to Pd) of triphenylphosphine, which helps keep palladium(0) fully complexed and thus in solution were used.[60] Thus the bromo arene (50f) was refluxed with the zinc reagent, 15% of the catalyst $Pd(PPh_3)_4$ and 30% of triphenylphosphine in THF for 42

hrs. The reaction was worked-up, which included a base extraction, to give a mixture of two compounds in a 52% yield: ibuprofen (1f), and phenylpropanoic acid[20] (24f) which arises from debromination (Scheme 47). The ^{1}H NMR spectrum of this crude mixture showed the resonances due to the propanoic side chain of ibuprofen, the doublet methyl which occurs at δ 1.49 and the benzylic quartet at δ 3.70. Under these signals was a doublet at δ 1.50 and a quartet at δ 3.74 which belong to (24f). The mass spectrum showed a strong peak at *m/e* 150 which corresponds to the molecular ion of (24f).



(50f) (1f) (24f)

Scheme 47

The rate limiting step of this reaction is the insertion of Pd into the Ar-Br bond. This rate is dependent on the concentration of triphenylphosphine–a higher concentration tends to keep all coordination sites on Pd occupied and thus slows the rate. The reaction was repeated with use of only a single additional equivalent of triphenylphosphine to cause Pd to coordinate less PPh_3. This was the case, 75% of the two compound mixture was recovered (approximately 80% of which was ibuprofen). These compounds were inseparable by chromatography when 2% acetic acid was used as a co-solvent. The solvent system ethyl acetate/hexane (1:1) has been used[6] to give separation of these types of compounds, although with poor recovery. Use of this solvent system gave spectroscopically pure ibuprofen in 50% yield. The ^{1}H NMR spectrum of this pure sample corresponded to that in the literature.[61]

Ibuprofen was derivatised with commercially available (*S*)-1-phenylethylamine (via the acid chloride) to form diastereomeric (*S*)-1-phenylethylamides, which were separable by HPLC. Integration of the HPLC peaks then gave the ratio of diastereomers and hence the ratio of enantiomers in the sample of ibuprofen. This analysis was kindly performed by P. J. Hayball, who developed the procedure.[44]

By this method, the product of asymmetric synthesis (*S*)-ibuprofen (1f) was determined to have an enantiomeric excess of 96%. This represents the minimum optical purity , as it is based on the assumption that the (*S*)-1-phenylethylamine has an optical purity of 100%. The loss of optical purity, from the >98% purity of the epoxide (25f) is consistent with the observation by Sharpless[54] that 2% racemisation occurs upon oxidation with ruthenium tetroxide.

In conclusion it was shown that (*S*)-ibuprofen can be synthesised in high optical purity by the Sharpless asymmetric epoxidation and a hydride based opening of the product epoxide. No chromatography, which would be costly on a larger scale, was used until purification of the final product–purification where necessary was carried out by crystallization.

The regioselectivity of the hydride opening of the epoxide was improved by finding a suitable solvent and with use of a greater number of equivalents of lithium borohydride. However the efficiency of this step is clearly still poor.

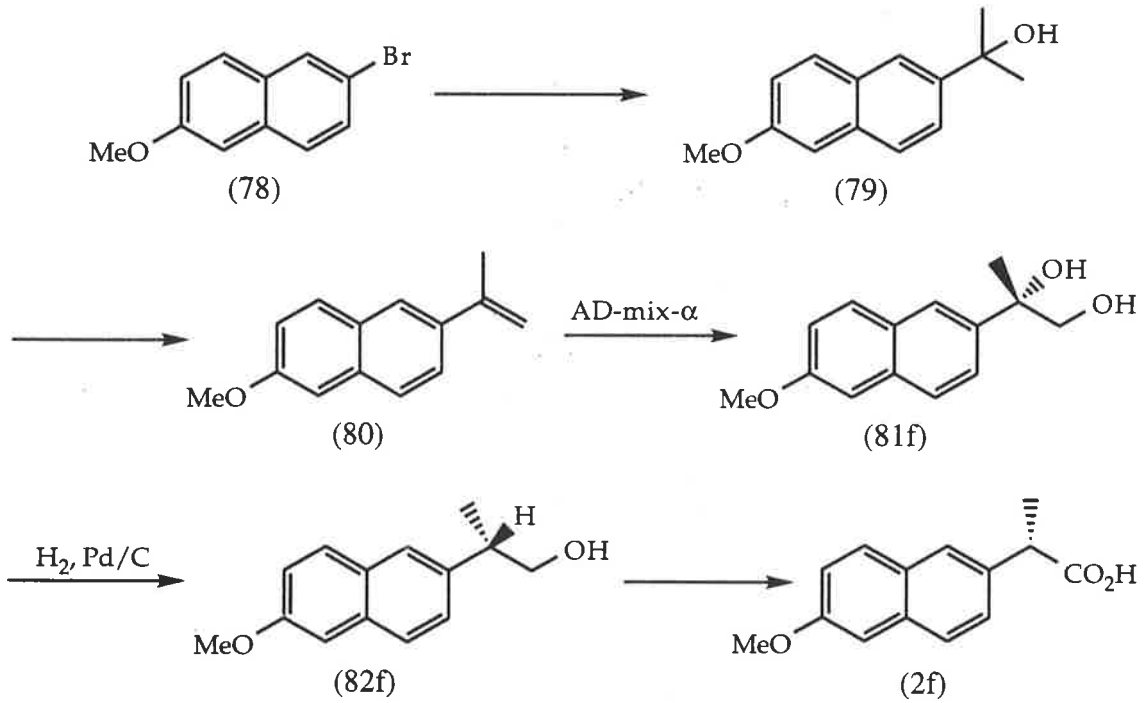
The coupling step gave an unexpected by-product. This could be avoided by modification of the conditions or with use of the corresponding iodo arene which is known to undergo coupling reactions more readily.[46]

If it was desired to investigate the concept of a common intermediate for arylpropanoic acids further, the use of the triflate group could prove fruitful. Subramanian[62] has shown that aryl nonaflates are not reductively cleaved under conditions which use Raney nickel as catalyst–conditions which stereo- and regioselectively hydrogenolyse benzylic epoxides (intro. p31). Also, aryl triflates are readily coupled to various organic groups by palladium catalysed coupling.[63] Thus the use of the corresponding aryl triflate could circumvent the problems listed for this synthetic route.

CHAPTER 2

ASYMMETRIC SYNTHESIS OF NAPROXEN

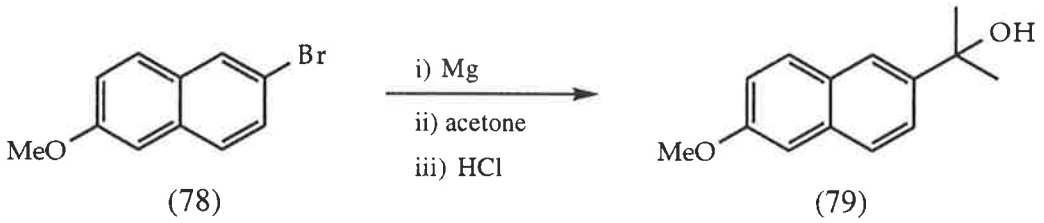
An overview of the proposed route is outlined in Scheme 48. The intention was to convert commercially available 2-bromo-6-methoxynaphthalene to the tertiary alcohol (79) which would then be dehydrated to the alkene (80). A Sharpless asymmetric dihydroxylation (AD) reaction of the alkene (80) would give the optically active diol (81f). It was expected that a stereoselective hydrogenolysis of (81f) over palladium catalyst would proceed with inversion of configuration to give the alcohol (82f) which could be oxidised to (*S*)-naproxen.



Scheme 48

A Grignard reaction was used to convert 2-bromo-6-methoxynaphthalene to the alcohol (79) (Scheme 49). Despite being a known compound[64] no procedure was available for its synthesis. It was found necessary to reflux the bromide (78) in ether over magnesium turnings for 18 h to convert it fully to the Grignard reagent. The magnesium turnings were activated by reaction with iodine for an hour, before addition of the bromide (78) which was sufficiently

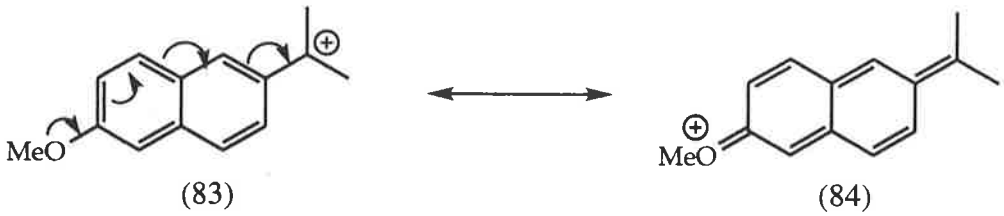
unreactive to be added, as the solid, in a single portion. Further activation of the magnesium was necessary by addition of a small amount of 1,2-dibromoethane before the reaction started. The Grignard reagent was quenched with acetone and then acidified with ammonium chloride solution to give the crude alcohol (79) which upon chromatography on silica gave the pure compound in yields of *ca.* 60%. The ^{1}H NMR spectrum of (79) is similar to the starting bromide with the addition of a 6H singlet at δ 1.66 due to the two methyl groups. The hydroxyl proton occurs at δ 2.04 as a broad singlet and the methoxy methyl as a 3H singlet at δ 3.91 and the complex 6H aromatic signal between δ 7.13-7.86.



(78) (79)

Scheme 49

The poor recovery of material was due to decomposition of the 3° alcohol during chromatography. The reason for the instability of this compound is due to the ready formation of the benzylic carbocation (83), delocalised onto the methoxyl oxygen which gives the highly stable oxonium ion (84) (Scheme 50).



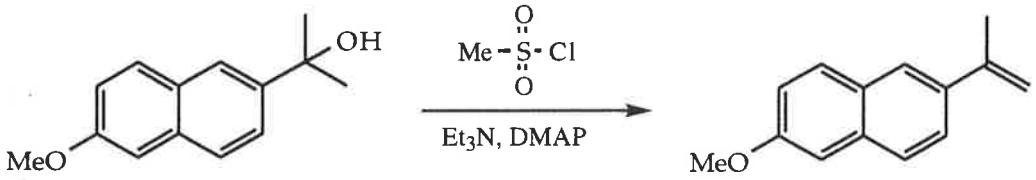
(83) (84)

Scheme 50

As decomposition occurred quite readily on both silica and alumina the crude material was used immediately in the next step and it was sufficiently pure for this purpose.

The next step in the synthesis was carried out according to the procedure by Yadav[64] who has performed the dehydration on this alcohol (79). Thus a solution of the alcohol (79) in dichloromethane and triethylamine with a catalytic amount of dimethylaminopyridine was treated with methanesulfonyl chloride to give the alkene (80) in yields of >85% (for this single

reaction) (Scheme 51) which was shown to be very pure by ^{1}H NMR spectroscopy. This alkene is also quite unstable and the crude material underwent decomposition during storage at -15°C as well as on silica and basic alumina during chromatography. Although a pure sample could be obtained by chromatography the recovery was poor. The ^{1}H NMR spectrum of this alkene shows a narrow, 1 Hz doublet, at δ 2.24 due to the methyl group; the methoxy methyl occurs as a singlet at δ 3.92; the *syn* to methyl alkene proton resonates at δ 5.14 as an apparent 1H quintet and the *trans* proton as a 1H doublet at δ 5.49, shifted downfield due to the proximity of the aromatic ring. The olefin protons are coupled to each other via (1 Hz). The aromatic region resonates at δ 7.11-7.78. This ^{1}H NMR data is consistent with that of Yadav.[64] The IR spectrum shows absorption at 1620 cm^{-1} due to the double bond. The melting point of the alkene is 104-106°C (no lit.[64] mp).



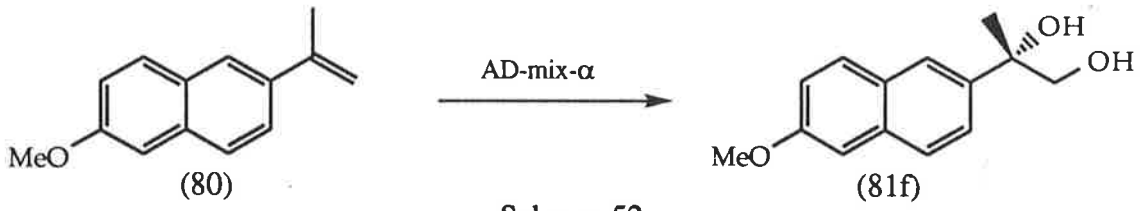
(79) (80)

Scheme 51

It was again found to be most efficient if the material is used directly, without purification, and immediately in the next step which is the Sharpless asymmetric dihydroxylation. Sharpless[65] has reported the conversion of (80) to the (*R*)-diol (81g) with an optical purity of 88% with use of the chiral ligand (DHQD)MEQ (59f) (p29). The AD reaction with this alkene has not been reported with the improved phthalazine class ligands.[35]

In the current work, the alkene (80) was treated with AD-mix-α, a commercially available mixture of the necessary reagents, including the ligand $(DHQ)_2$-PHAL, to give the optically active diol (81f) (Scheme 52). When performed on purified alkene all peaks in the ^{1}H NMR spectrum of the crude product could be accounted for in terms of the expected diol (81f), thus the methyl protons resonate as a singlet at δ 1.58 and the OH protons at δ 2.2 and δ 2.9, each as a broad singlet. Two doublets at δ 3.67 and δ 3.85 arise from the diastereotopic C$\underline{H}_2$O protons which have an 11 Hz geminal coupling. The C$\underline{H}_3$O protons resonate as a singlet at

δ 3.92 and a complex 6H signal between δ 7.11 and δ 7.85 is consistent with the aromatic protons. The only other signal present in this spectrum of the crude material is due to the methyl group of *t*-butanol at δ 1.25; while the OH was too broad to be visible.



(80) (81f)

Scheme 52

The diol is unstable on neutral alumina and upon chromatography of the crude material to remove the ligand the diol was recovered in only 45% yield.

When these three reactions are carried out without purification of any intermediates, a yield of 85% of the crude diol (81f) was obtained. The ^{1}H NMR spectrum of this material surprisingly shows it to be of high purity (Figure 20). Chromatography of the crude material with dichloromethane/ethyl acetate on alumina followed by recrystallization from ether/hexane gave the diol (81f) as white crystals, with a melting point of 107-108°C but in a yield of only 53%.

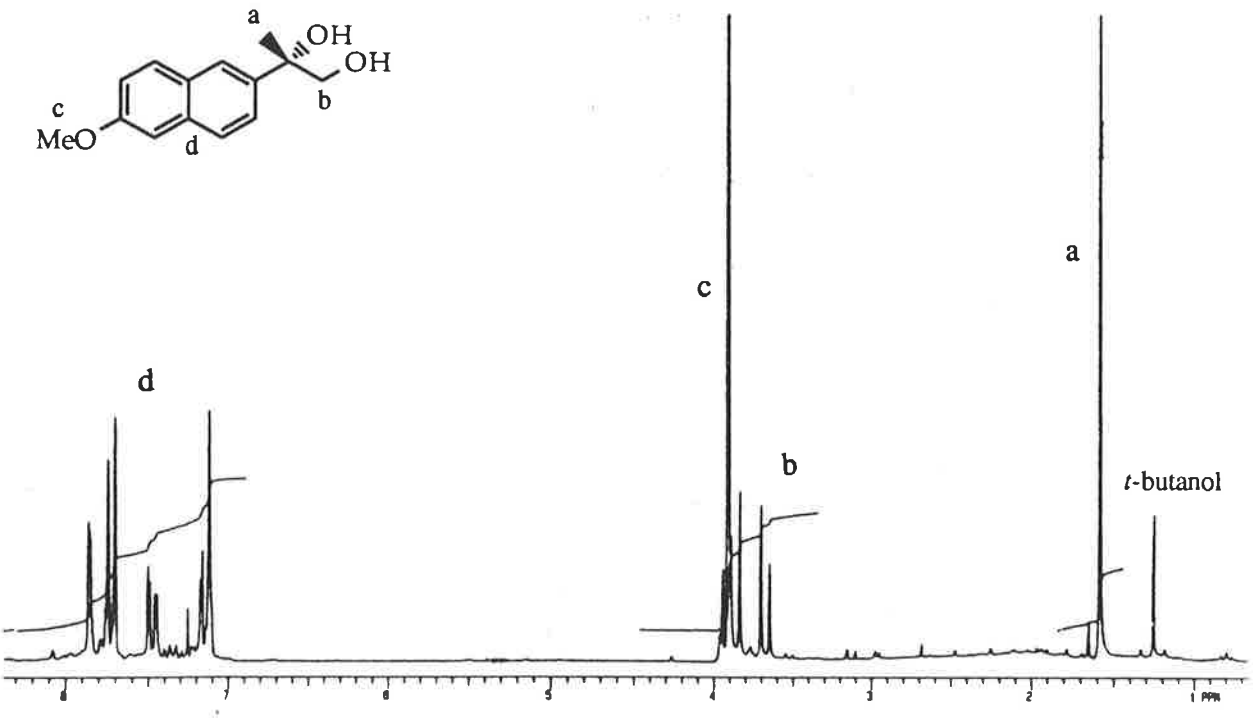
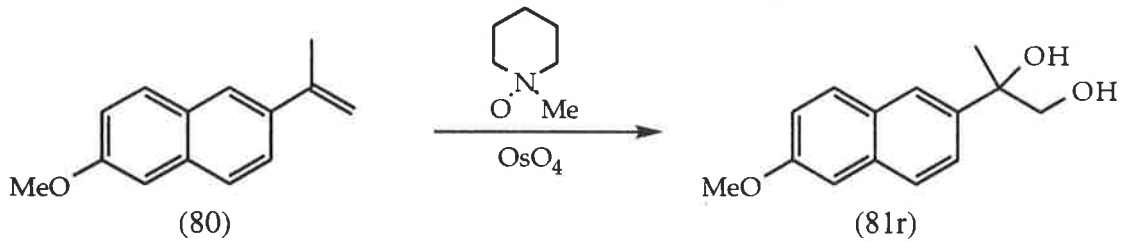


Figure 20

It likely that triethylamine as co-solvent for chromatography would have limited the amount of decomposition of these compounds. Another possibility is the direct recrystallization of the crude solid diol (81f), as impurities are minimal. However these options were not considered at the time.

To determine the optical purity of the diol (81f), a sample of the racemate (81r) was required as a standard. This was obtained by oxidation of (80) with an excess of *N*-methylmorpholine oxide and a catalytic amount of osmium tetroxide (Scheme 53), in accordance with the general procedure of VanRheenen[66]. The racemic diol (81r) was obtained in 61% yield and had identical ^{1}H NMR data with those of the purified optically active analogue (81f).

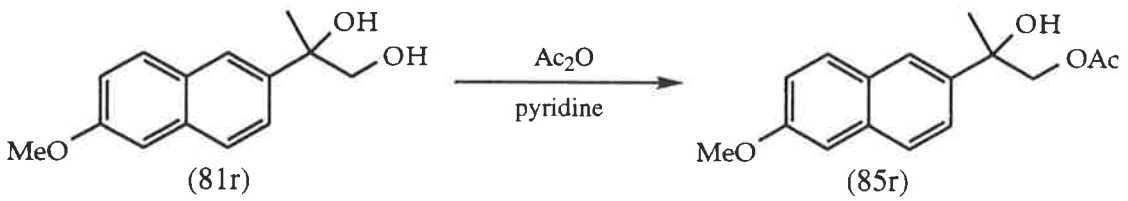


(80) (81r)

Scheme 53

A sample of the racemic diol (81r) was converted to the acetate (85r) with an excess of acetic anhydride in pyridine (Scheme 54). No acetylation of the tertiary hydroxyl group was observed.

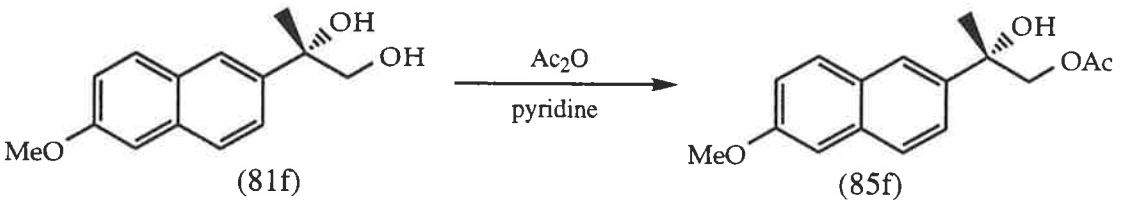
The acetate (85r) was analysed with the chiral shift reagent tris[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorato] europium(III) derivative. The anaylsis was performed on the acetate because of past experience in this group,[6] with this shift reagent had indicated that a free primary hydroxyl group in substrates of this type can give rise to line broadening in the ^{1}H NMR spectrum before satisfactory separation of peaks due to the diastereomeric interaction of the enantiomers. The methyl of the acetate singlet can also be a diagnostic peak since often it separates into narrow singlets.



(81r) (85r)

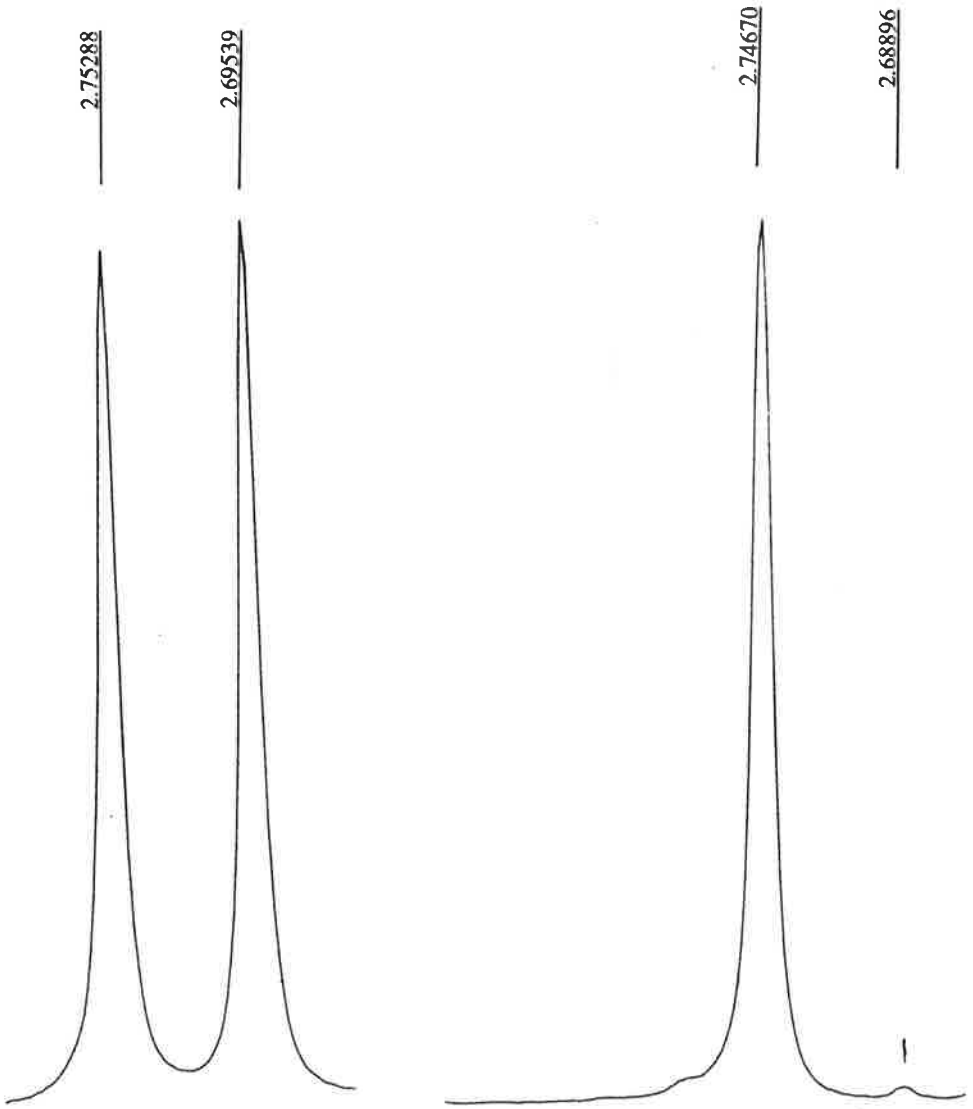
Scheme 54

The ^{1}H NMR spectrum of the acetate (85r) shows a singlet at δ 1.63 due to the methyl group attached to the chiral centre and another at δ 2.03 due to the acetate methyl group. The methylene protons appear at δ 4.29 and δ 4.39 as two 11 Hz doublets and the aromatic protons resonate as a complex signal at δ 7.11-7.87 ~~with~~ while the methoxy methyl protons occur at the usual δ 3.91. Upon the addition of enough of the chiral shift reagent to a solution of the racemic acetate (85r) in carbon tetrachloride containing sufficient deuterobenzene to allow the spectrometer to be locked (*ca.* 15%), each of the methyl singlets moved downfield and separated into two singlets. An approximate one-to-one ratio on a weight-to-weight basis of substrate to shift reagent was found to be optimal. This caused the acetate methyl singlet originally at δ 2.03 to appear as two peaks at δ 2.70 and δ 2.76 and the methyl singlet at δ 1.63 to appear as two peaks at δ 2.52 and δ 2.57. This effect is due to the diastereomeric interactions of each enantiomer in the racemate with the optically active reagent and is shown, for the acetate methyl, in Figure 21a. The signals due to the acetate methyl were more diagnostic than those of the methyl attached to the stereogenic centre.



Scheme 55

In a similar manner a sample of the optically active diol (81f) from the Sharpless asymmetric dihydroxylation reaction was converted to the acetate (85f) (Scheme 55). Under similar conditions to those used for the analysis of the racemate (85r), a carbon tetrachloride/d-benzene solution of (85f) was treated with the chiral shift reagent. The acetate methyl region of the resultant ^{1}H NMR spectrum is reproduced in Figure 21b. ~~Electronic~~ Integration indicated that the enantiomers were present in a ratio of 99:1, or that the optical purity of the diol (81f) was 98%.

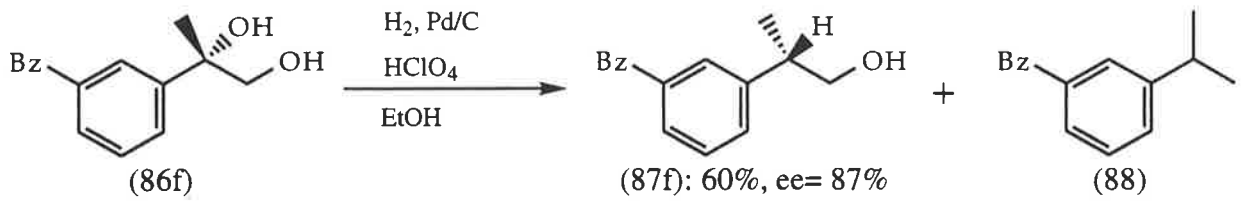


a) racemic b) optically active

Figure 21

The next step of the synthesis required hydrogenolysis of the benzylic hydroxyl group of (81f) with control of stereochemistry. Work performed by Newton[6] in this group has shown that the corresponding *m*-benzylphenyl diol (86f) can be hydrogenolysed to the optically active alcohol (87f) with palladium on carbon catalyst (Scheme 56). It was found necessary to use a catalytic amount of perchloric acid[38] to effect the reaction, otherwise only starting material was recovered. Perchloric acid has been reported to greatly enhance the rate of hydrogenolysis of

benzylic hydroxyl groups without causing racemisation.[67] The reason for the rate increase being the leaving ability of the benzylic group, which in the system $PhCH_2OR$ increased in the order OH < O-alkyl < O-aryl < OH^+alkyl < OH_2^+ < OAc < $OCOCF_3$ for hydrogenolysis.[38]

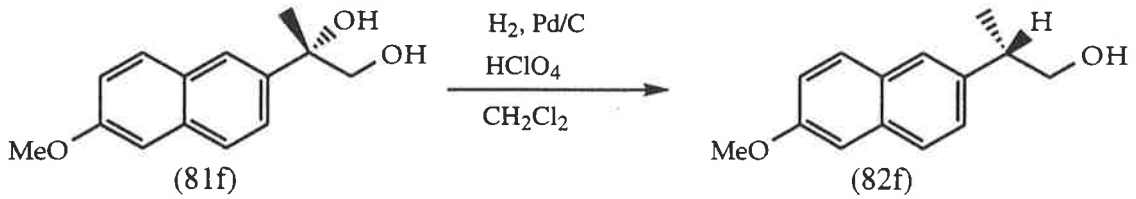


(86f) (87f): 60%, ee= 87% (88)

Scheme 56

Both yield and stereoselectivity were dependent on solvent, and ethanol was the solvent of compromise of three tested, including dichloromethane and ethyl acetate. The desired diol (87f) was obtained in 60% yield and with an optical purity of 87% when this solvent was used. The fully deoxygenated compound (88) formed the remainder of the product material.

The diol (81f) was subjected to similar conditions. Thus it was stirred for 3 days in dichloromethane under hydrogenolysis conditions in the presence of perchloric acid to give the crude product (82f) in 98% yield which ^1H NMR spectroscopy indicated contained some starting material (Scheme 57). Since there was no septet in the ^1H NMR spectrum it was clear the deoxygenated product corresponding to (88) did not arise. Chromatography on silica gave pure alcohol (82f) in 55% yield. The ^1H NMR spectrum showed the methyl as a doublet at δ 1.33 and the benzylic proton at δ 3.06 as a sextet. The hydroxyl appears at δ 1.5, the diastereotopic methylene protons now appear as a doublet at δ 3.74 and again the methoxyl methyl resonates at δ 3.90, and the aromatic protons form a multiplet at δ 7.10-7.71.



(81f) (82f)

Scheme 57

The hydrogenolysis reaction was repeated with ethyl acetate however the ^{1}H NMR spectrum of the crude product mixture was more complex and the yield of the alcohol (82f) after chromatography was only 24%.

This hydrogenolysis reaction was however variable, sometimes giving a product mixture of which none of the components could be identified. The cause of this could not be identified–two different batches of diol (82f) gave widely varying results despite no obvious difference in purity, as indicated by ^{1}H NMR spectroscopic analysis of these batches.

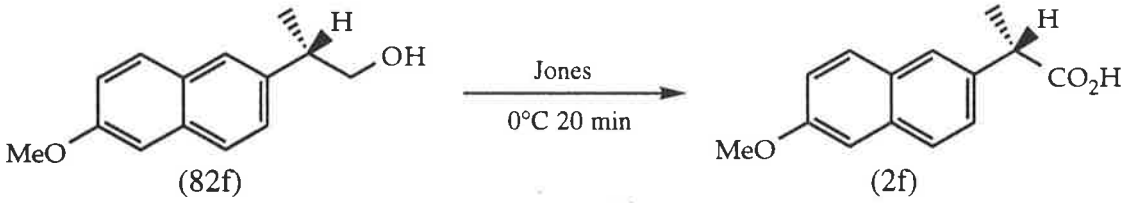
To test methods for the determination of optical purity of the alcohol (82f) a sample of the racemic material (82r) was also needed. Thus a sample of the racemic diol (81r) was placed under similar conditions as above, with dichloromethane as solvent, and gave (82r) in a yield of 60% after chromatography. Diastereomeric carbamates[68] were prepared from the racemic diol (81r), however, these were found to be not suitable for the determination of optical purity either by TLC analysis (to test whether HPLC analysis can be used) or ^{13}C NMR spectroscopic analysis[68]. The Mosher esters were later found to be effective for the determination of optical purity of this alcohol. This was however not known at the time.

The final step was oxidation of (82f) to naproxen (2f), and this was attempted with the ruthenium trichloride/sodium periodate oxidizing system.[53] The ^{1}H NMR spectrum of the crude product mixture was very messy and the TLC showed streaking which indicates that polymerisation had occurred. It is possible that the labile nature of the benzylic position is the cause of problems here that were not encountered in other systems.

The alcohol (82f) was placed under 'purple benzene' oxidation conditions.[69] Thus to a benzene/water co-solvent which contains potassium permanganate and the phase-transfer catalyst *tetra*butylammonium bromide was added the alcohol (82f) and the mixture stirred 18 h. These conditions failed to give the carboxylic acid and mostly starting material was recovered.

Jones' conditions[70] were found to give naproxen in 20 min at 0°C, whereupon the reaction was quenched with thiosulphate solution and bicarbonate (Scheme 58). The carboxylic acid was purified by extraction with base. Upon acidification naproxen was recovered in 95% yield. The ^{1}H NMR spectrum showed a high degree of chemical purity, the methyl appears as a doublet at δ 1.58, the benzylic proton at δ 3.86 as a quartet, and the methoxy naphthalene group appears similar to that found earlier, which corresponds to the literature.[71] The IR spectrum shows absorption at 1700 cm^{-1} due to carboxylic acid C=O stretching.

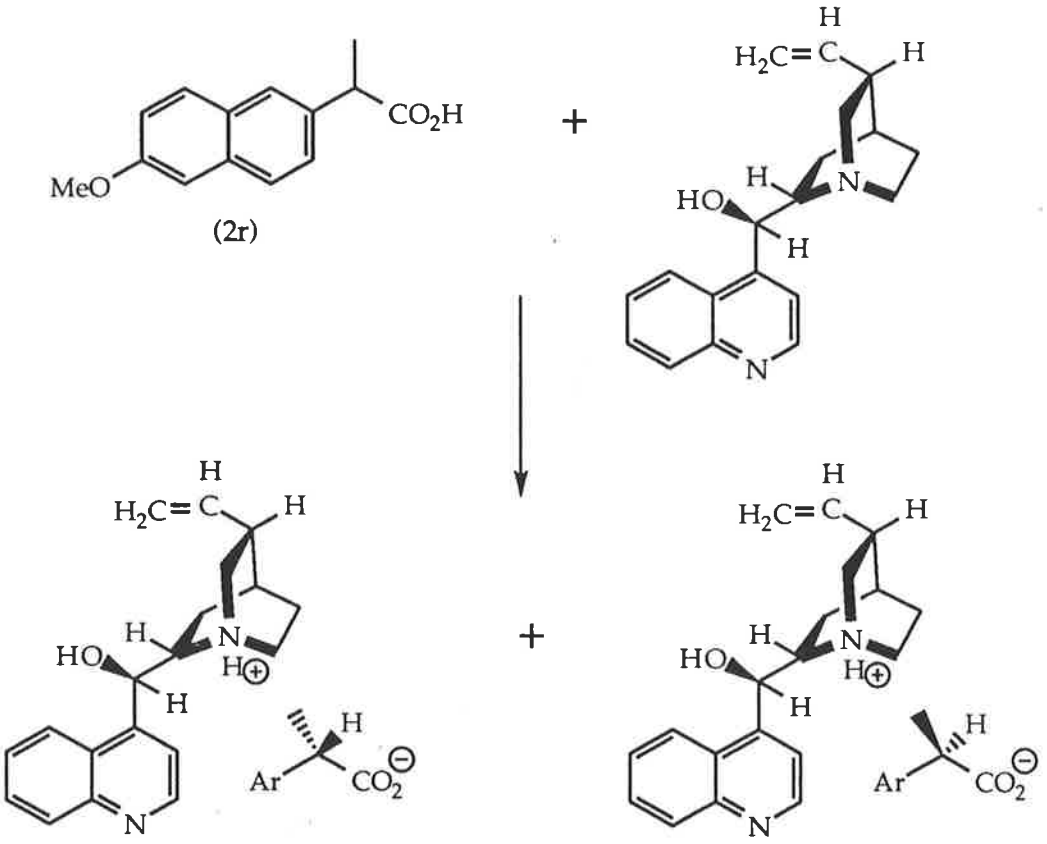
The alcohol (82f) used here came from a hydrogenolysis reaction in ethyl acetate solvent.



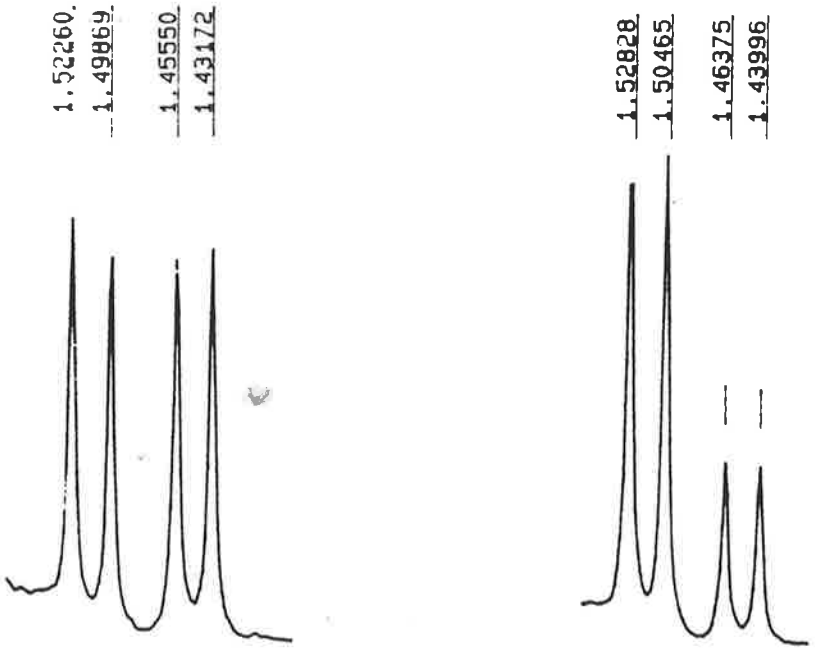
(82f) (2f)

Scheme 58

The racemic sample of naproxen was also obtained via Jones' oxidation. The enantiomers of naproxen could be differentiated by formation of diastereomeric salts with optically active cinchonidine (see also intro. p15) in a solution of d-chloroform (Scheme 59).[6,18] The methyl resonances in the ^{1}H NMR spectrum of the diastereomers (89) and (90) are distinct (Figure 22a). The optically active naproxen sample was analysed under the same conditions and by electronic integration an e.e. of 47% (Figure 22b) was found, which, considering that the diol was 98% optically pure, is clearly very poor. The stereogenic centre could have partially racemised either during the hydrogenolysis reaction, which Newton[6] has shown proceeds with a lack of stereochemical purity, or during the oxidative conditions. Of the two, it seems more likely that the ready formation of the delocalised carbocation may form in the presence of aqueous perchloric acid to cause partial racemisation before the substrate is on the surface of the catalyst.



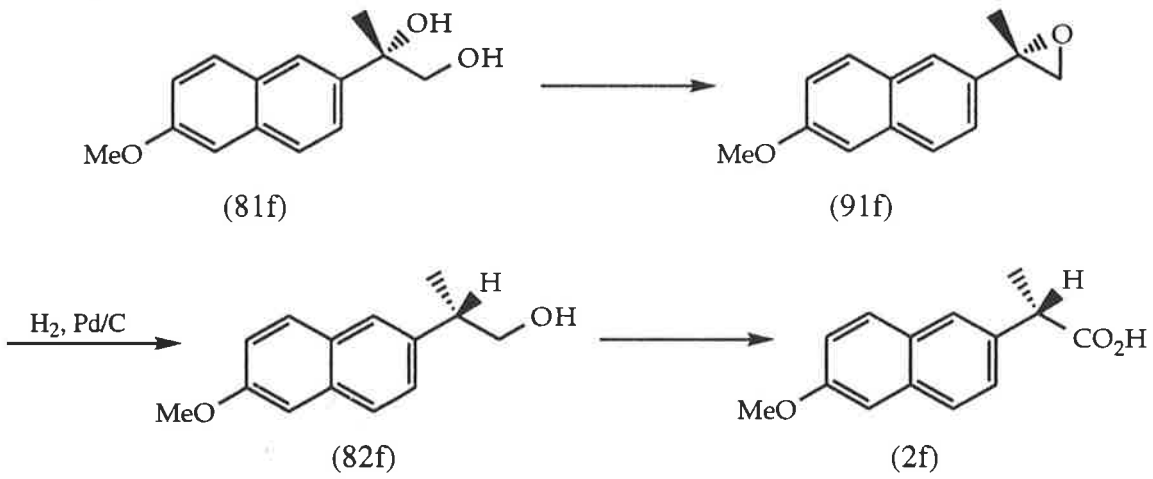
Scheme 59



a) racemic b) optically active

Figure 22

At this point it was decided to modify the synthetic route to overcome the problems associated with the hydrogenolysis of the diol. As hydrogenolysis of benzylic epoxide C-O bonds proceeds very readily and with high stereoselectivity without the presence of acid catalyst it was considered that the epoxide (91f) would be a better compound through which to obtain the alcohol (82f) (Scheme 60). This could be expected to give the alcohol (82f) in high stereochemical and chemical purity. The final step of the synthesis remains the same.

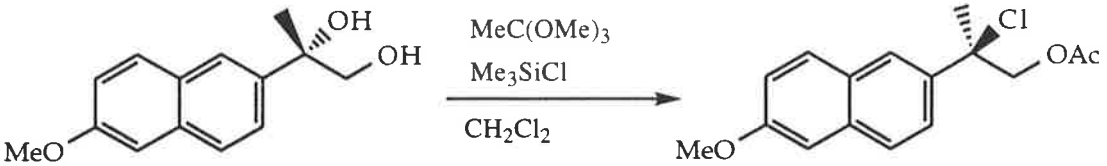


Scheme 60

The formation of the epoxide (91f) was attempted according to the conditions Sharpless has developed for the conversion of diols into epoxides.[72] This two step process occurs with two inversions of the stereochemistry at the benzylic position, the epoxide is then formed with the same configuration as the starting diol. This reaction is very general, although limitations include sterically crowded diols which give unsatisfactory results, and partial racemisation which may occur with electronically activated diols, both of which are characteristics of the current diol (81f). Nevertheless the conditions developed by Sharpless were tried.

The diol (81f) was stirred at room temperature in the presence of trimethylorthoacetate and trimethylsilane for 3 hr before the product (92f) was recovered by evaporation of excess reagent and solvent (Scheme 61). The ^{1}H NMR spectrum showed the conversion was clean, the two methyl groups were apparent at δ 2.04 and 2.09, and the methylene AB quartet has moved downfield to δ 4.56, the remainder of the spectrum was similar to previous

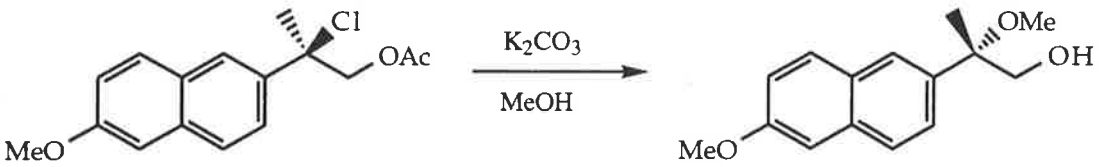
compounds. The IR spectrum shows a strong stretching absorption at 1730 cm^{-1} due to the acetate carbonyl and the mass spectrum shows the loss of Cl'.



(81f) (92f)

Scheme 61

Reaction of this chloro acetate (92f) with potassium carbonate in methanol was expected to furnish the epoxide (91f), however in the ^1H NMR spectrum of the product of this reaction the methylene group appears at δ 3.59 and is also coupled to a neighbouring exchangeable proton, whereas epoxide protons occur more upfield at δ 2.6 and no vicinal coupling was expected, there is also a singlet at δ 3.17 consistent with the methoxyl resonance. The mass spectrum showed a molecular ion at *m/e* 246. Thus the product was likely the methoxy hydroxy species (93f) shown (Scheme 62). That this product can form is not unreasonable as the benzylic carbocation forms easily, and would quickly be quenched by methanol.

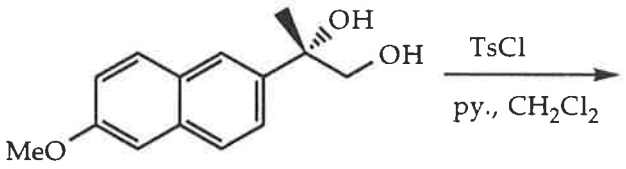


(92f) (93f)

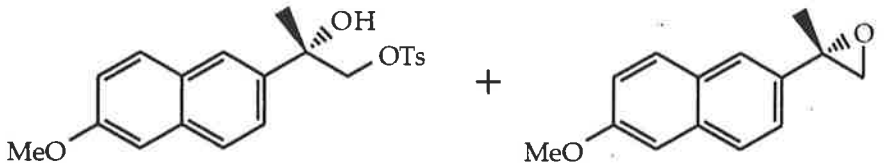
Scheme 62

Another way to form the epoxide could be via the primary tosylate, which is expected to undergo intramolecular substitution to give the corresponding epoxide with retention of configuration at the benzylic centre.[73] Reaction of the diol (81f) with tosyl chloride at room temperature for 18 hr, with pyridine (5 equiv) in dichloromethane gave a product mixture, TLC analysis of which showed, contained two compounds (Scheme 63). The reaction mixture was loaded directly onto a column of silica made from a slurry with 1:1 hexane/dichloromethane to which 5% triethylamine had been added to remove acidic sites, and eluted with this solvent. The ^1H NMR spectrum of the high Rf compound showed resonances that corresponded to

those expected for the epoxide (91f): a 2H AB quartet at δ 2.95 and a 3H singlet at δ 1.80 as well as the methoxy and aromatic protons which occurred in the usual position. The low Rf compound, which occurs as a yellow band on silica, was the tosylate (94f) (Scheme 63). The ^{1}H NMR spectrum of the eluted product showed the methyl protons of the propyl chain at δ 1.63, the methyl protons of the tosyl at δ 2.39, the methoxyl resonance at δ 3.91. The methylene protons absorb at δ 4.16 as a singlet and the aromatics occur in the usual position. The mass spectrum shows the molecular ion at *m/e* 386 as well as a peak for the loss of the tosylate group.



(81f)



(94f) (91f)

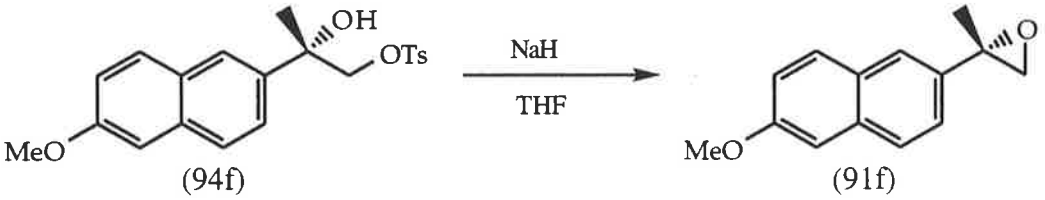
Scheme 63

The elimination of the tosylate (94f) to form the epoxide (91f) which is usually performed with hydride as base[73] has occurred here with the weak base, pyridine. An attempt was made to see whether the elimination to the epoxide could be completed by increased concentration of pyridine and longer reaction time, however all this seemed to do was decompose the epoxide.

Yields of epoxide, based on the diol (81f) were between 80-90%.

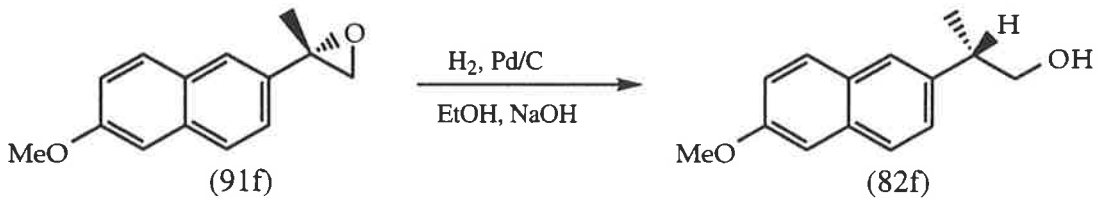
Reaction of a mixture of tosylate (94f) and epoxide (91f) with sodium hydride in dry THF gave the epoxide (91f) in variable amounts as shown by ^{1}H NMR spectroscopy. This reaction is very sensitive to water. The epoxide is found in a high degree of purity and yields of 80% when the conditions are completely anhydrous (Scheme 64). However, a trace amount of water, which forms sodium hydroxide, a good nucleophile, decomposes the entire material to the extent that nothing of the product mixture was identified by ^{1}H NMR spectroscopy. Water

presumably entered this reaction sometimes through condensation of atmospheric moisture on solvents during the process of setting up the reaction, despite precautions taken to ensure anhydrous conditions. Excess sodium hydride was used, as hydride is a poor nucleophile and will not cause decomposition of the epoxide. Recrystallization of the epoxide from hexane gave fluffy white crystals of mp 86-88°C.



Scheme 64

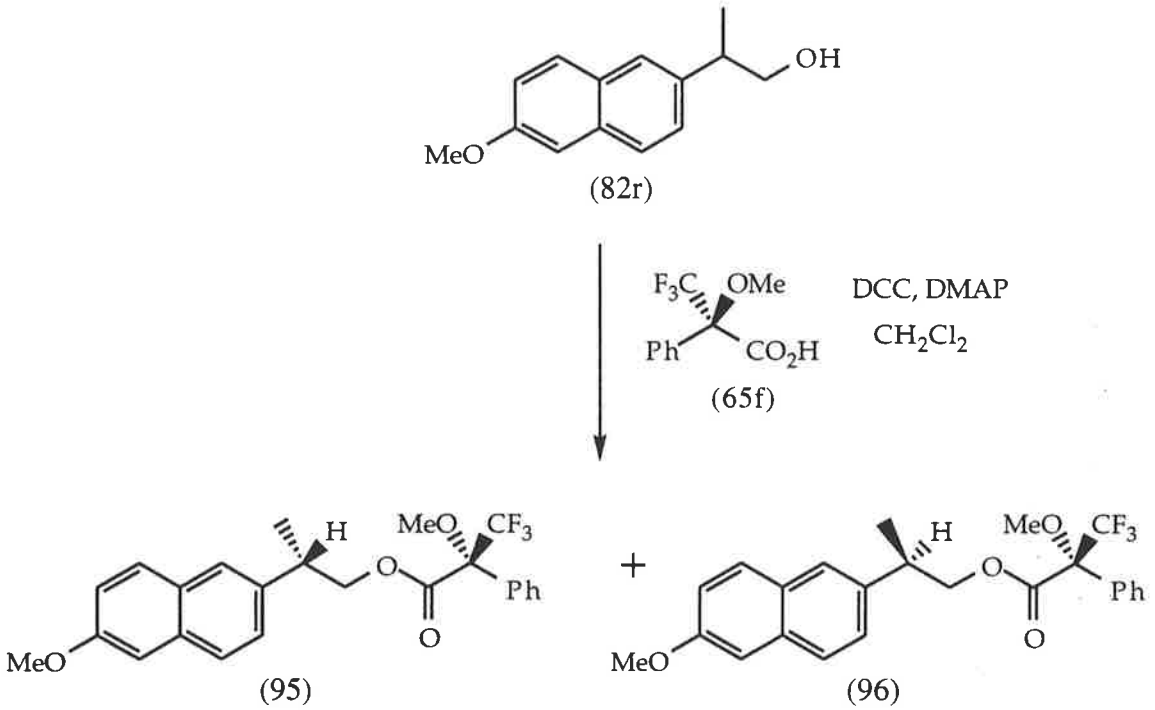
The epoxide (91f) was hydrogenolysed using the conditions of Sugi,[42] who has researched room temperature hydrogenolyses of a 1-phenyl-1,2-epoxycyclohexane. The conditions used were, 10% palladium on carbon catalyst under a hydrogen atmosphere in ethanol as solvent with one drop of 10% sodium hydroxide solution (Scheme 65). Filtration to remove the catalyst and evaporation of the solvent gave the alcohol (82f) in 92% yield. A portion was recrystallized from ether/hexane of give powdery crystals of mp 82-4°C (lit.[75] mp 88-9°C). The ^{1}H NMR spectrum of this crude product shows it to have a high degree of purity. The main features of the spectrum were that the methyl resonance now appears as a doublet at δ 1.33, the benzylic proton appears as a sextet at δ 3.07 and the methylene proton as a doublet at δ 3.75.



Scheme 65

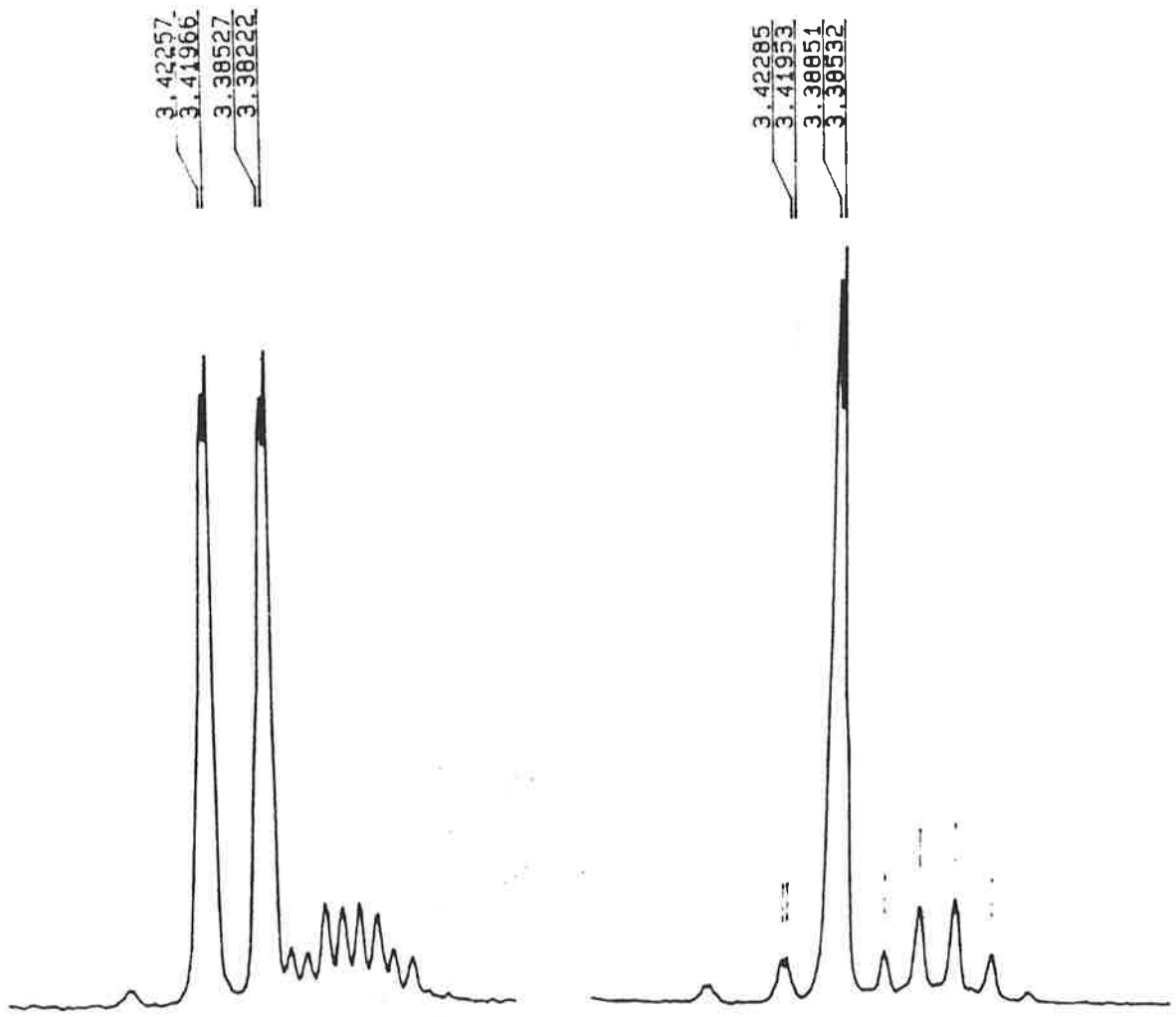
The racemic epoxide (91r) was similarly hydrogenolysed at room temperature, and the product (82r) was recovered in 88% yield. Recrystallization of this racemic alcohol from hexane gave material melting at 90-91°C

The method of detection of the enantiomers (82f) and (82g) that was pursued this time was the formation of the diastereomeric Mosher esters (95) and (96) from optically pure Mosher's acid (65f) (Scheme 66). Thus according to the general procedure of Hassner[74] a solution of the alcohol (82r), (4.0 mg), and an excess of (65f) and *N,N*-dicyclohexylcarbodiimide in dichloromethane with a catalytic amount of dimethylaminopyridine was stirred at room temperature for 18 hr. A normal aqueous work-up followed by chromatography on silica gave the diastereomeric mixture of esters in 70% yield.



Scheme 66

The ^1H NMR spectrum of this mixture of diastereomers showed some resonances were non-coincident, in particular the methoxyl groups α to the CF_3 were separate peaks with about baseline separation. One signal resonates at δ 3.37 and the other at δ 3.40, and they both show 1.1 Hz ^1H-^{19}F long range coupling (Figure 23a). The methine sextets at δ 3.30 overlap, while the methylene doublets of doublets at δ 4.38 and 4.58 could be distinguished but were not as useful as the methoxyl resonances which could be used reliably to determine the enantiomeric excess of the optically active sample .



a) racemic b) optically active

Figure 23

Under similar conditions as used above for (82r), the optically active alcohol (82f) was esterified. The work-up was modified such that the reaction mixture was loaded directly onto a column of silica, ~~which~~ This gave the diastereomers, which are coincident on silica, in 77% yield. ~~Electronic~~ Integration of the methoxy peaks in the ^{1}H NMR spectrum (Figure 23b) corresponding to the two enantiomers showed the optical purity of this alcohol to be 89%. This value was further confirmed by use of the cut-and-weigh method of integrating the area under the peaks.

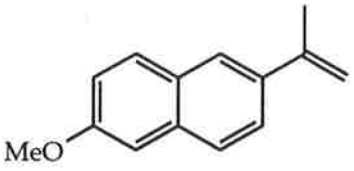
The alcohol (82f) was oxidized with Jones' reagent at 0°C for 20 min as previously described (p68) to give naproxen in a lower yield of 55%. A ^{1}H NMR spectroscopic analysis of the

diastereomeric salts formed, as described above, with one equivalent of cinchonidine followed by cut-and-weigh integration of the methyl doublet resonances indicated an enantiomeric excess of 91% which is within experimental error of 89% and indicated no loss of optical purity during the oxidation step.

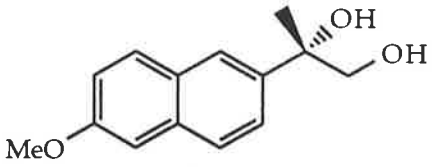
Since the optical purity of the diol (81f) was shown to be 98%, and the tosylation should not effect the chiral centre, the purity was clearly most likely lost during the hydrogenolysis reaction. Hydrogenolysis at a lower temperature was expected to give better stereoselectivity and therefore this reaction was repeated at -40°C with stirring for 18 hr. The alcohol (82f) was recovered from this reaction in 92% yield and was converted to the Mosher ester as previously described. ^{1}H NMR spectroscopic analysis indicated an optical purity of 97% ee.

This sample was oxidized to naproxen (2f), 2 mg of which was recrystallized (hexane/acetone) to give fine white crystals of melting range 151-153°C (lit.[75] mp 152-154°C). The analytical procedure with the cinchonidine salts indicated an enantiomeric excess of 96% which may be within experimental error of 98% e.e. or it is possible that 2% of the sample racemised during the last two reactions .

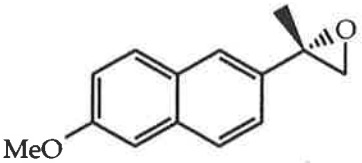
In conclusion it has been demonstrated that the chiral propanoic acid side chain of the drug (*S*)-naproxen can be synthesized with high optical purity. The route is via the alkene (80) which can be synthesized readily from commercially available starting material. This alkene undergoes the Sharpless asymmetric dihydroxylation to introduc~~reactions are~~ optical activity giving the diol (81f) in 98% ee. The diol is converted to the epoxide (91f) which is hydrogenolysed with palladium on carbon at low temperature to the alcohol (82f) with little if any loss of optical purity. Finally, oxidation using Jones' reagent gave (*S*)-naproxen (2f) also without any detectable loss of optical purity. The yields were respectable for all reactions give the products in high chemical purity, once the condtions were ~~sufficiently~~ optimized.



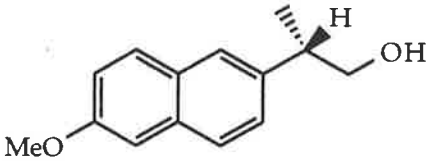
(80)



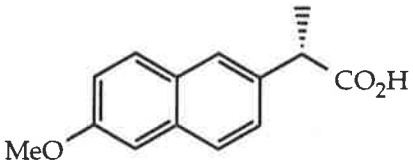
(81f)



(91f)



(82f)



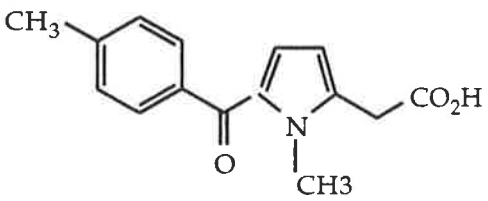
(2f)

CHAPTER 3

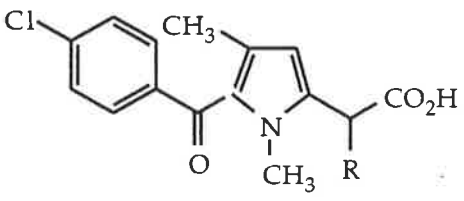
ATTEMPTS TOWARDS THE ASYMMETRIC SYNTHESIS OF KETOROLAC

(*S*)-Ketorolac (3f) (Figure 24) is a non-steroidal agent with potent analgesic and moderate anti-inflammatory activity.[76] The racemic form is already commerically available. It is the only NSAID which is marketed for intramuscular administration and is being promoted as an effective postoperative analgesic drug; hence, generally for short term use only.

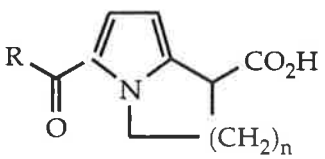
Tolmetin (97) and zomepirac (98) (Figure 24) are two pyrroleacetic acid derivatives which are employed in the relief of rheumatoid arthritis and pain. These compounds were chosen by Muchowski as a starting point for structural modifications. It was found by Carson[77] that methylation of zomepirac (98) in the acetic acid side chain as in (99) markedly increased the anti-inflammatory potency. It was therefore not illogical to expect that the rigid bicyclic framework that would result from the inclusion of the carbon atoms corresponding to the N- and C-methyl groups of (99) in a cyclic system (i.e. 100) might be associated with an increase in anti-inflammatory potency. Of the over 100 variations of (100) tested for anti-inflammatory and analgesic activity three compounds–(101), (102) and ketorolac (3)–were found to be sufficiently potent to be further developed.



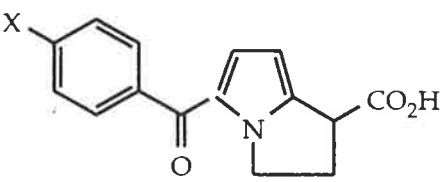
(97)



(98) R = H, (99) R= CH_3



(100)

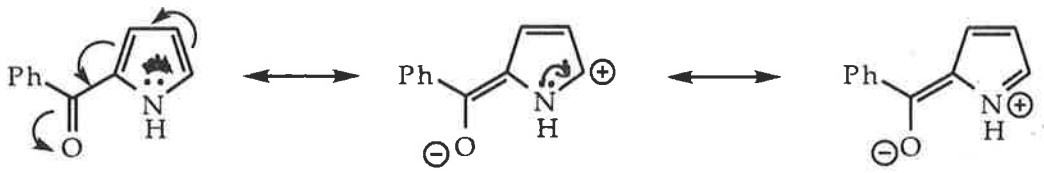


(3), X= H (101), X= CH_3
(102), X= CH_2=CH_2

Figure 24

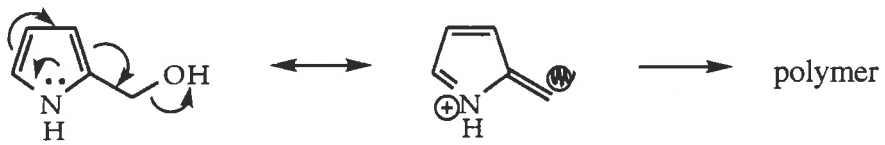
A similar route to that used to obtain naproxen was planned–which makes use of the Sharpless asymmetric dihydroxylation and catalytic hydrogenolysis reactions to control stereochemistry. As a synthetic challenge ketorolac is significantly different despite this similar route, due to the greater instability of pyrrole compounds.

Pyrrole is a "π-excessive" 5-membered heterocycle with six π-electrons delocalized over the ring. It undergoes electrophilic substitution much more readily than benzene; substitution normally occurs preferentially at the α position. A group that withdraws electron density by resonance and is in conjugation with the pyrrole ring will leave the ring insufficiently electron dense to allow facile attack by an electrophile (Scheme 67). Electron-withdrawing groups may also change the orientation of substitution on the pyrrole ring; for example, an electron-withdrawing substituent at the α position leads to electrophilic substitution at the β positions.[78]



Scheme 67

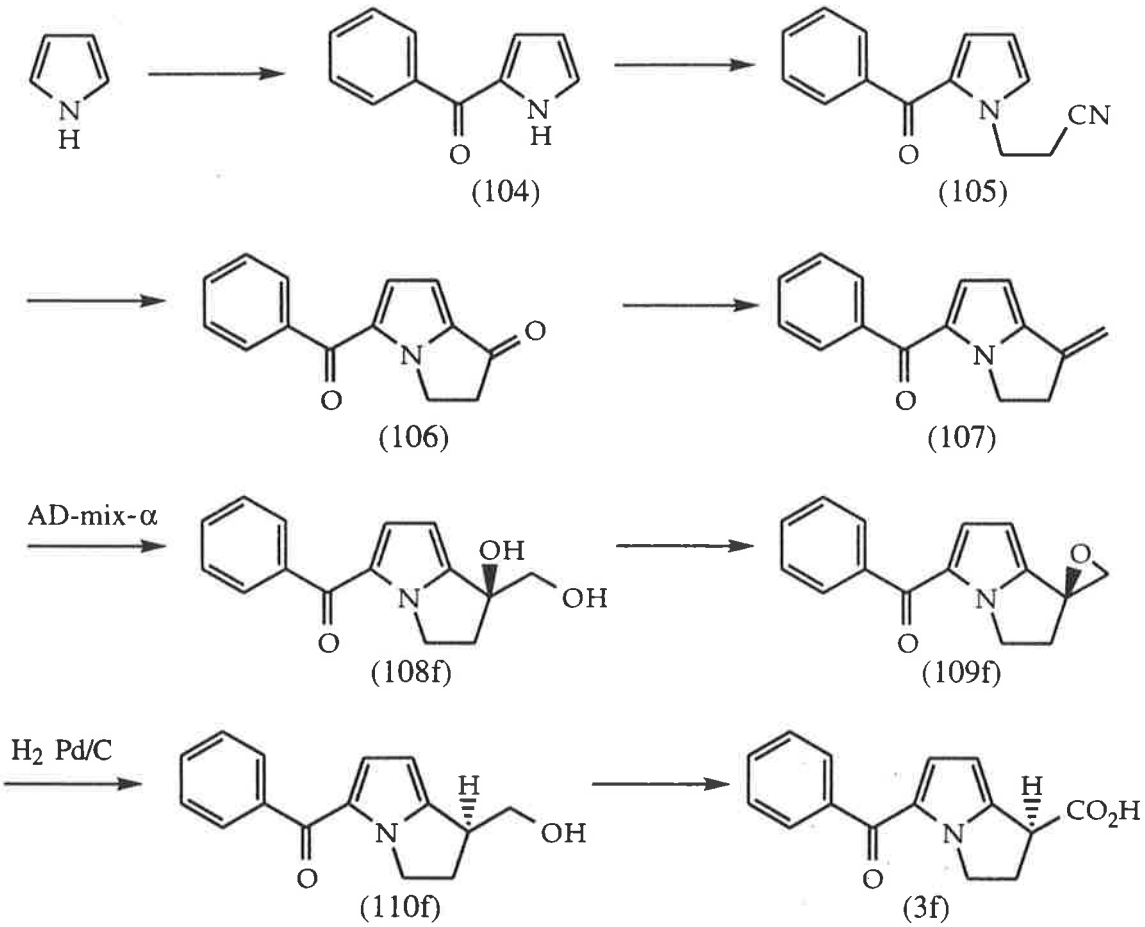
Pyrrole systems are otherwise quite labile, especially pyrrole carbinol type systems where a hydroxyl or similar group adjacent to the ring is readily displaced to give the reactive species (103) which polymerises instantly (Scheme 68). These types of systems were a planned part of the synthesis of ketorolac and as such the benzoyl group was planned to be in place from the start of the synthesis, for the purpose of stabilization of the pyrrole ring.



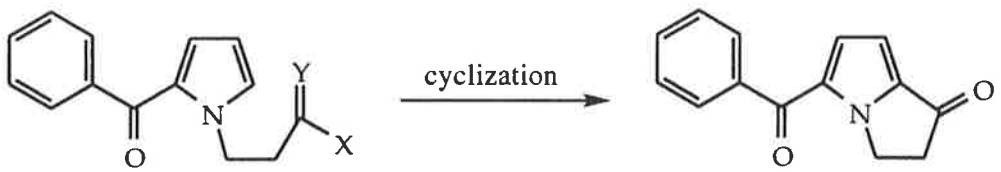
(103)

Scheme 68

The benzoyl group would thus give the pyrrole ring added stability, however, may make it so stable as to render it inactive to electrophilic substitution.



Scheme 69a



X, Y= certain electronegative atoms

Scheme 69b

The benzoyl group was planned to be in place from the start of the synthesis, for the purpose of stabilization of the pyrrole ring (Scheme 69a). It was expected that the diketone (106) could be synthesized by the following short procedure (Scheme 69a). The Vilsmeier-Haack reaction would furnish 2-benzoylpyrrole (104) to which a functionalized alkyl chain such as the 2-cyanoethyl group could be attached to give (105). Appropriate cyclization conditions to close the ring could give the desired diketone.

From the diketone (106) the exocyclic olefin (107) would be prepared, and this used in the Sharpless asymmetric dihydroxylation reaction to give the optically active diol (108f). This diol could be converted to the epoxide (109f) which could undergo regio- and stereoselective catalytic hydrogenolysis of the benzylic C-O bond to give the alcohol (110f) which could be oxidized to ketorolac (3f).

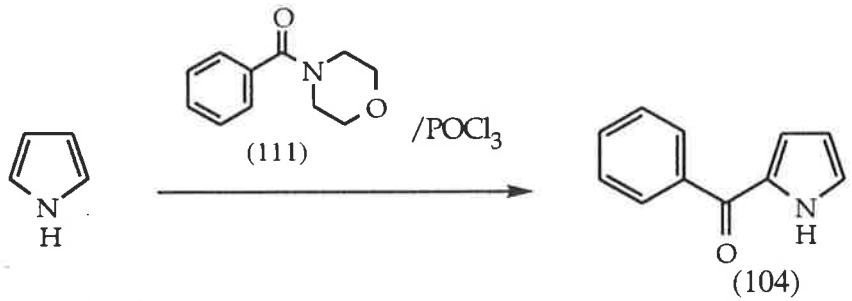
The diketone (106) was to be the initial target molecule from which asymmetric chemistry could be explored. The cyclization step was expected to be difficult as the benzoyl group deactivates the pyrrole ring to further electrophilic substitution. Other groups that could be used to induce the terminal carbon to be electrophilic include the amide and acid chloride functional groups. The different conditions used to polarise these groups may be more appropriate for this specific molecule (Scheme 69b). This compound (106) has previously been prepared only by the degradation of ketorolac itself.[79] The conditions used were to heat a sealed, basic solution of ketorolac that had been saturated with oxygen at 100°C. The ^{1}H NMR spectrum of the diketone (106) is thus known.

The diketone turned out to be unusually hard to obtain by constructive synthesis due the deactivation of the pyrrole ring by the carbonyl group. Many routes were tried, however the diketone could not be made efficiently. Other routes to ketorolac were eventually tried and these are described later in the chapter.

The formation of 2-benzoylpyrrole (104) was carried out according to the refinements made to the Vilsmeier-Haack conditions by McGillivray.[80]

The amide, benzoyl morphilide (111) was prepared by dropwise addition of morpholine to a solution of benzoyl chloride and triethylamine in toluene. Recrystallization of the recovered amide resulted in long thick needle crystals in an 84% yield.

The benzoylating agent was prepared by reaction of the amide (111) with phosphoryl chloride, whereupon pyrrole in dry dichloroethane was added. After the solution was stirred for 24 h an increase in absorption in the 350 to 400 nm region of the UV spectrum of the reaction mixture indicated that the reaction was complete (Scheme 70).



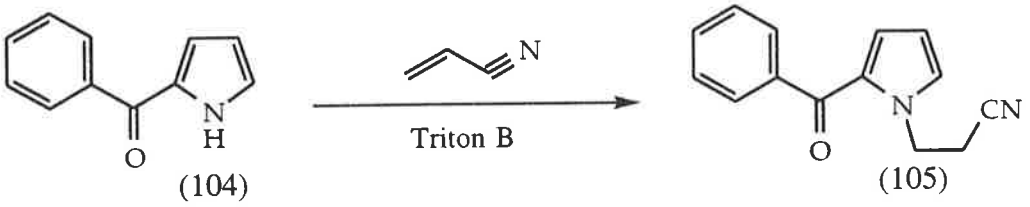
Scheme 70

The reaction was neutralised by cautious addition of 20% sodium carbonate solution to the vigorously stirred solution. The recovered pale red solid was recrystallized from hexane to give pale pink crystals of the pyrrole (104) of melting range 72-79°C (lit.[81] mp 79°C) in an overall yield of 66%. The mother liquor was evaporated and the residue together with a red oil which precipitated during the recrystallization was eluted through a short column of silica to give a further quantity of 25% yield of (104) as a pale pink solid. Thus the required product (104) was obtained in better than 90%. The ^{1}H NMR spectrum of (104) showed three double doublet resonances due to pyrrole hydrogens at δ 6.33, 6.89 and 7.18; the NH proton appeared at δ 10.6 as a broad singlet. The phenyl group resonated between δ 7.41-8.01. The IR spectrum showed carbonyl absorbtion at 1620 cm^{-1}.

An excess of activated reagent was used in this reaction and on work-up the amide (111) was re-liberated. This caused problems with the purification–some product could be obtained

directly by recrystallization, however chromatography was complicated by the similar Rf of the product and the amide. The ^{1}H NMR spectrum of the amide is deceptive as it is an apparent singlet for the aromatic protons and broad unresolved signals due to the morpholine group. In fact, it was not realised for some time that the product considered to be (104) was contaminated with the amide (111).

To prevent this problem in future preparation of benzoyl pyrrole (104) it would appear well to use excess pyrrole substrate to completely consume the activated amide. The excess pyrrole in the product mixture could presumably be removed by recrystallization or chromatography. However, this possibility has not been investigated.



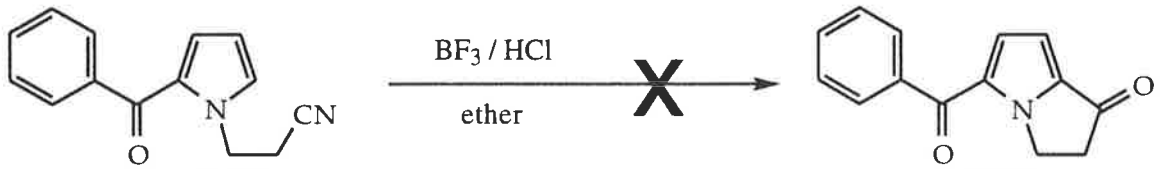
(104) (105)

Scheme 71

According to the conditions used by Patterson[82] for unsubstituted pyrrole, 2-benzoylpyrrole with acrylonitrile in the presence of a catalytic amount of Triton B (35% benzyltrimethylammonium hyroxide in methanol) produced the crude cyanoethylated product (105) in quantitative yield (Scheme 71). The mixture was chromatographed to remove more polar material but attempts to recrystallize from a hexane/dichloromethane solvent system were not successful as heat induced decomposition occurred quickly, with decomposition material precipitating continuously from the hot solution. Thus the material with melting range of 82-87°C could not be further purified. The ^{1}H NMR spectrum of the nitrile (105) is similar to that of 2-benzoylpyrrole with the additional presence of two triplets at δ 4.61 and 3.02 and the absence of the pyrrolic peak at δ 10.6. The IR spectrum showed absorption at 2250 and 1620 cm^{-1} due to the nitrile and the carbonyl functional groups respectively.

The product (105) was then subjected to the cyclization conditions reported by Patterson[82] for *N*-(2-cyanoethyl)pyrrole (112) (Scheme 73), in an attempt to obtain the diketone (106). The Lewis acid, boron trifluoride etherate was added to a solution of the nitrile (105) in dry ether

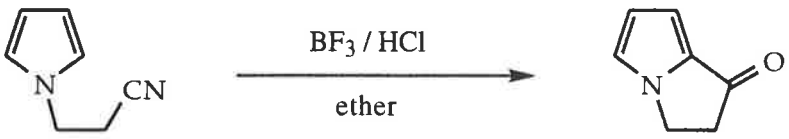
and the solution saturated with dry hyrogen chloride gas and allowed to stir in a stoppered flask for 2 days (Scheme 72). Work-up involved removal of the acid catalysts and solvent under reduced pressure. Following the procedure developed by Patterson to hydrolyse the intermediate imine, chloroform and 28% ammonia solution were added to the residue and the mixture refluxed for 18 hr. Recovery of the pyrrolic product material followed by removal of polymeric material by chromatography resulted in a 20% recovery of starting material as seen by ^{1}H NMR spectroscopy. There was no evidence that any cyclization had taken place.



(105) (106)

Scheme 72

In order to determine whether the experimental conditions had been correctly applied, the compound, cyanoethylpyrrole (112), cyclized by Patterson in 30% yield, was subjected to the these conditions (Scheme 73). A modification was however made in the work-up where an aqueous solution of sodium acetate was used to hydrolyse the intermediate imine rather than ammonia solution. The desired product (113) was recovered quantitatively, and cleanly, as shown by ^{1}H NMR spectroscopy; three double doublets occur at δ 6.52, 6.73 and 7.04; the two methylene groups resonate at δ 3.08 and 4.31. The IR spectrum shows the carbonyl absorption at 1700 cm^{-1} and the complete absence of the nitrile absorption.



(112) (113)

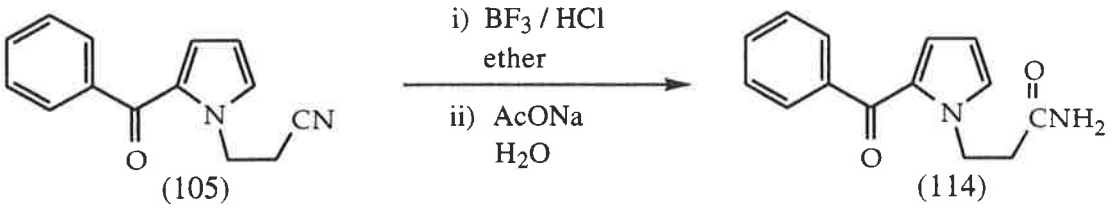
Scheme 73

Clearly these conditions worked for the normal pyrrole. It therefore appears that the benzoyl group deactivates the pyrrole ring to such an extent that electrophilic substitution does not

occur under these conditions. It also shows that the conditions of hydrolysis used by Patterson were too vigorous since a better yield results under the milder conditions.

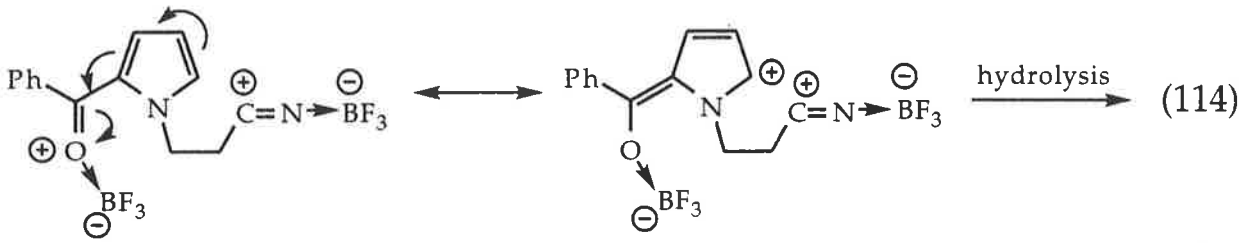
The nitrile (105) was re-subjected to the acidic conditions (Scheme 74). This time, however, sodium acetate was used in work-up. A different result was obtained, to give the amide (114) which was shown to be quite pure by ^{1}H NMR spectroscopy, again with no sign of the cyclized product (106); the ^{1}H NMR spectrum of the amide (114) is similar to that of the nitrile (105) with the addition of the broad NH singlets at δ 5.5 and 6.0. The IR spectrum shows the NH absorptions at 3350 and 3153 cm^{-1}, carbonyl amide absorptions at 1700 and 1690 cm^{-1} and ketone absorptions occur at 1620, 1610 and 1600 cm^{-1}.

It appears that the expected Lewis acid/base complex between the nitrile and boron trifluoride did form during this reaction and was hydrolysed to the amide in work-up; this complex did not form in the first trial reaction, possibly due to insufficient hydrochloric acid catalyst.



Scheme 74

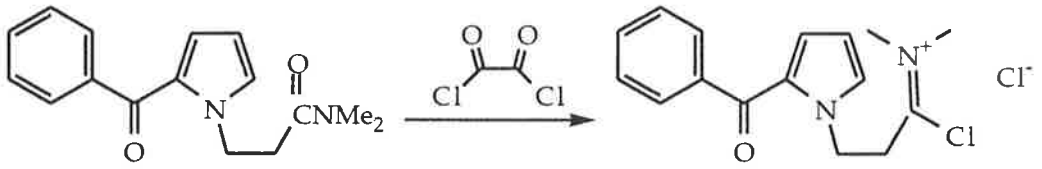
It seems probable that the carbonyl, which is in conjugation with the pyrrole ring, bonds to boron trifluoride and this withdraws electron density from the pyrrole ring, to leave it insufficiently electron dense to be attacked by the electrophilic cyano/boron trifluoride complex on the terminal carbon (Scheme 75).



Scheme 75

In attempt to obtain the bicyclic system, the dimethylamide functional group was tried next. The dimethylamide functional group has the potential to be activated selectively. The amide (115) can be seen to have two amide functional groups, i) the less reactive vinylogous amide, which incorporates the benzylic carbonyl and the pyrrole ring, and ii) the dimethylamide. Selective activation would leave the ketone free and thus electron density would not be withdrawn from the pyrrole ring by this means.

Thus a route should be found to the amide (115), and following general conditions used by Muchowski[83] to activate this by Vilsmeier-Haack conditions to give the intermediate (116) which is analogous to an acid chloride functional group with attached Lewis acid (Scheme 76).

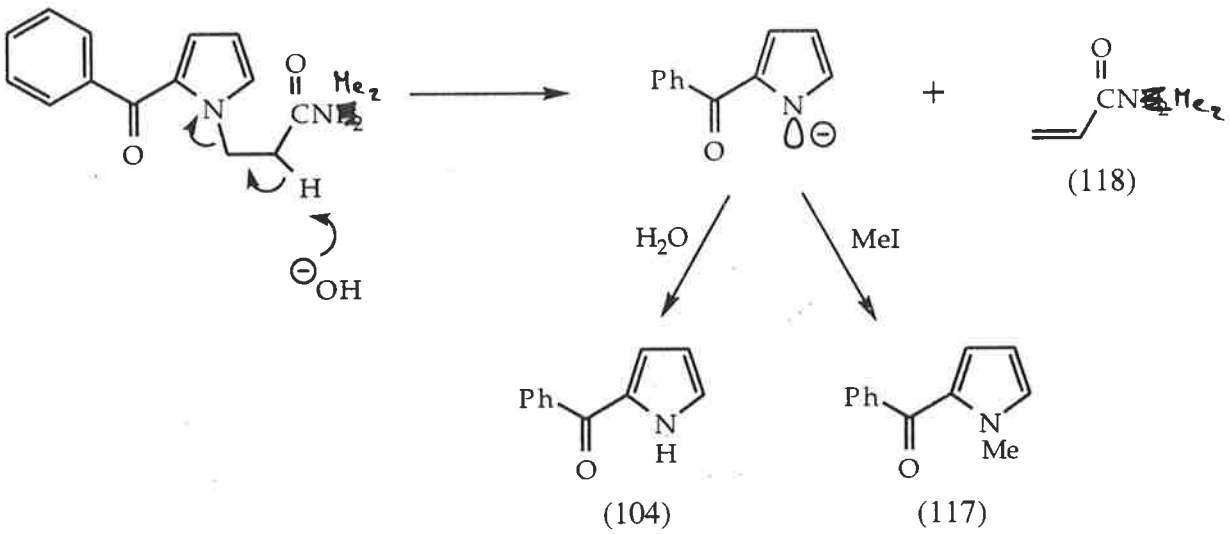


(115) (116)

Scheme 76

A quick route to the amide (115) would be via hydrolysis of the nitrile (105) to ~~the~~ give unsubstituted amide followed by methylation. The hydrolysis step was attempted unsuccessfully by heating the nitrile in concentrated hydrochloric acid/THF solution at 40°C for 2.5 hours.[84] An aqueous solution of triflic acid in THF with 18 hr reflux and other methods of hydrolysis were also unsuccessful. Thus the amide was prepared via the unwieldy conditions discovered in the unsuccessful cyclization attempt. The amide (114) was recovered from the reaction as a dark red solid which was purified by elution through a short column of flash silica in 74% yield. Further purification of the material was effected by recrystallization from water, with a hot filtration to remove insoluble red material, to give yellow needle crystals in 40% yield, shown to be quite pure by ^{1}H NMR spectroscopy. The amide melted in the range of 151-160°C after starting to decompose at *ca.* 110°C.

Methylation[85] of the amide (114), to give (115), was attempted by reaction of the amide with methyl iodide in a solution of potassium hydroxide in DMSO for 15 minutes. The reaction was worked up by addition of ammonium chloride and removal of the DMSO by distillation under high vacuum. The crude material contained two products as shown by TLC, which, after separation by flash chromatography, were identified by ^{1}H NMR spectroscopy as 2-benzoylpyrrole (104) and 1-methyl-2-benzoylpyrrole[86] (117). These two products have arisen by elimination of the propylamide chain after the α-hydrogen is removed by hydroxide to give the nitrogen based anion which reacts with either methyl iodide or a proton (Scheme 77).



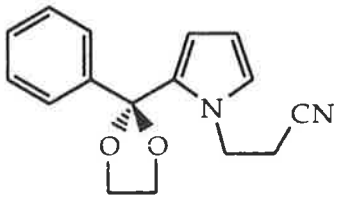
Scheme 77

An attempt was therefore made to prepare the methylated amide (115) in a similar manner to that used for the preparation of the nitrile (105)–by the reaction of 2-benzoylpyrrole with *N,N*-dimethylacrylamide (118). The reagent (118) was prepared by treatment of acryloyl chloride with dimethylamine gas and the crude product was shown to be sufficiently pure by ^{1}H NMR spectroscopy to be used without further purification.

A solution of 2-benzoylpyrrole and the acrylamide (118) in dioxane which contains a catalytic amount of the base Triton B, failed to produce any of the desired *N*-alkylated amide (115). Substitution of sodium hydride as the base and DMF as a co-solvent also failed to produce the amide. These failed reactions show that the separate pyrrole (104) and acrylamide

are more thermodynamically stable than the desired product. It was again decided to try a different tactic.

To protect the carbonyl of the nitrile (105) and thus take it out of conjugation with the pyrrole ring would presumably allow the cyclization to proceed under the conditions of Patterson.[82] It was presumed that this could be done by formation of the acetal (119).



(119)

The protection was attempted according to the general procedure by Eliel[87] which uses one equivalent of ethylene glycol and a catalytic amount of *p*-toluenesulphonic acid. This mixture was refluxed in toluene through a Dean-Stark trap for 4 hours. After work-up in which the reaction mixture was washed once with 10% sodium hydroxide solution and three times with water, to remove the acid catalyst and excess glycol, and dried over anhydrous sodium carbonate, it was found by ^{1}H NMR spectroscopy that the carbonyl remained completely unprotected. It was thought that the acetal had been formed but was destroyed in the aqueous work-up procedure as the carbocation formed in the deprotection step is doubly benzylic and as such readily formed. The liberated glycol although not seen in the ^{1}H NMR spectrum could have been completely washed out with water.

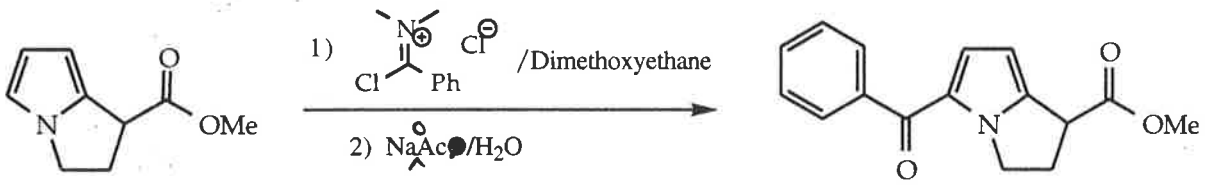
The reaction was repeated this time with an anhydrous work-up, which simply involved removal of toluene by distillation, first at atmospheric pressure then under reduced pressure. The ^{1}H NMR spectrum of the crude material showed the presence only of the starting ketone, with no sign of acetal formation or of ethylene glycol. It was considered that glycol was removed from the reaction mixture by formation of an azeotrope with toluene (93.5/6.5 ratio for the toluene/glycol azeotrope[88]), while the doubly benzylic and hindered ketone was too unreactive to form the acetal. Under these conditions it was also possible that a trace amount of base, possibly the amphoteric glass surface, was neutralizing the acid catalyst. It was

thought these problems may be overcome by use of benzene as the reaction solvent, which may less effectively azeotrope the glycol, although no data was found, and use of 0.2 equivalents of acid catalyst.

These reaction conditions were applied with 3 equivalents of ethylene glycol and the work-up carried out under anhydrous conditions, benzene was removed under reduced pressure. The crude residue was analysed by ^{1}H NMR spectroscopy which showed that starting ketone was the main component of a mixture which contained decomposition material.

Another possibility along this line would be formation of a thioacetal, which should form more readily but also might be correspondingly harder to remove (this route was however not followed).

Muchowski[83] has successfully benzoylated the pyrrolopyrrole (120) (Scheme 78) with use of Vilsmeier-Haack type chemistry–*N,N*-dimethylbenzamide (122) activated with oxalyl chloride. This was stirred in a polyether solvent for 40 hr at 50°C to give the benzoylated material (121).

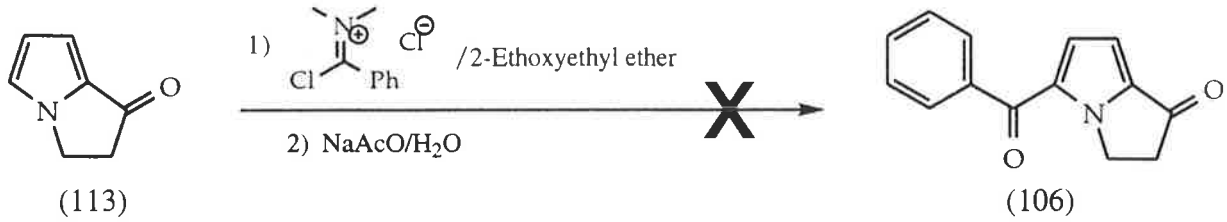


(120) (121)

Scheme 78

The ketone (113) on which this reaction would be attempted has the carbonyl group in conjugation with the pyrrole ring and as such this substrate is less reactive than (120).

A solution of the amide (122) in polyether solvent was reacted with oxalyl choride at room temperature for 2 hr before it was heated at 50°C to complete the reaction. Excess oxalyl chloride was removed under vacuum to give a solution of the activated complex in polyether solvent. Ketone (113) was added as a solid and the mixture heated under dry conditions for 40 hr at 55°C (Scheme 79). The reaction was quenched by basic hydrolysis conditions to give the pyrrolic mixture, which ^{1}H NMR spectroscopy indicated contained only starting ketone (113) and *N,N*-dimethylbenzamide.



(113) (106)

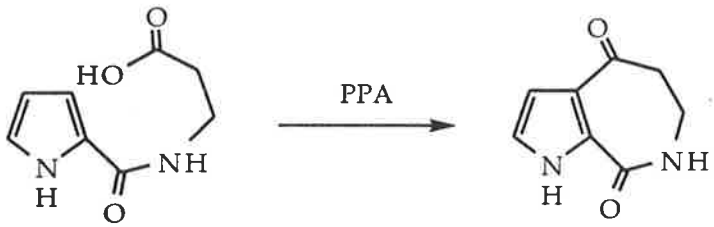
Scheme 79

The reaction was repeated at 140°C for 40 hr, however the result was no more favourable, the ^{1}H NMR spectrum indicated the presence of starting materials and some polyether solvent.

It was not realised at the time that phosphoryl oxychloride forms the more reactive benzoylating agent than oxalyl chloride[83] and would have been more suitable for this deactivated pyrrole.

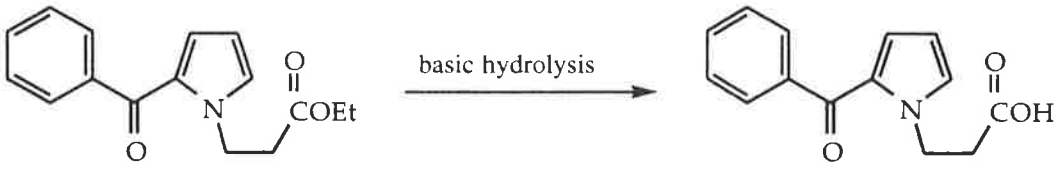
It was next attempted to form the diketone (106) via the carboxylic acid functional group on the *N*-alkyl chain.

Cyclization to form a 7-membered ring attached to pyrrole has been achieved by Kasum[89] in 57% yield from the corresponding carboxylic acid by reaction with polyphosphoric acid (Scheme 80).



Scheme 80

The ester (123) (Scheme 81) was prepared in the usual manner with ethyl acrylate and a catalytic amount of Triton B. It was obtained in a crude yield of 96% as a low-melting off-white solid which was of high purity as seen by ^{1}H NMR spectroscopy and used without further purification. The spectrum was similar to that of the nitrile (105) with the addition of a 2H quartet at δ 4.13 and a 3H triplet at δ 1.23 due to the ethyl group. The IR spectrum shows absorption at 1730 and 1610 cm^{-1} due to the ester and ketone C=O bonds respectively.



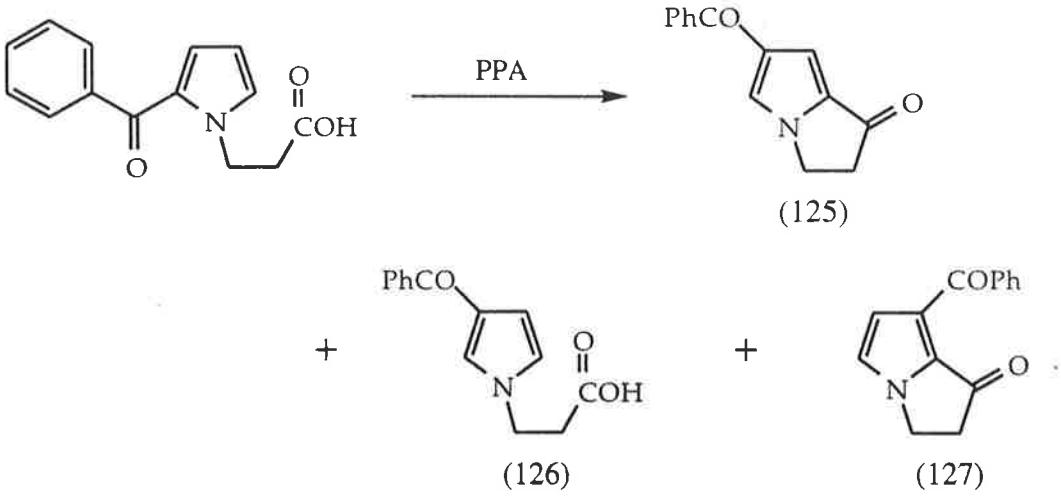
(123) (124)

Scheme 81

The ester underwent smooth basic hydrolysis to yield the acid (124) (Scheme 81) which was recrystallized from water after decantation of the hot solution from an insoluble red oil. The acid was obtained in 95% yield, as white crystals of mp 114-116°C. The ^{1}H NMR spectrum was similar to that of the nitrile (105) and the IR spectrum showed absorption at 1730 and 1620 cm^{-1} due to the carboxylic acid and the ketone C=O bonds respectively.

The acid (124) was subjected to the conditions reported[89], thus it was heated in polyphosphoric acid at 100°C for 30 minutes, followed by work-up with solid sodium carbonate (Scheme 82). The resultant basic aqueous solution was extracted to give 10% of a compound, the ^{1}H NMR spectrum of which shows two triplets at δ 3.14 and 4.41 due to the two methylene groups. Two doublets at δ 7.11 and 7.64 due to the pyrrole protons indicate that cyclization has occurred. The aromatic signals extended from δ 7.45 to 7.78. These types of resonances are the same as those of the desired diketone (106)[79] however the chemical shifts are different. The molecular weight was determined by mass spectroscopy to be *m/e* 225, the same as that of the diketone (106), which implies an isomer of this compound and hence rearrangement.

The remainder of the material was recovered by acidification of the basic aqueous phase and extraction. This acidic material had similar ^{1}H NMR resonances to the starting acid (124), the chemical shifts were, however, different. MS established that the molecular mass was the same as that of the starting acid (124) which ~~indicated~~ implies that rearrangement had occurred.

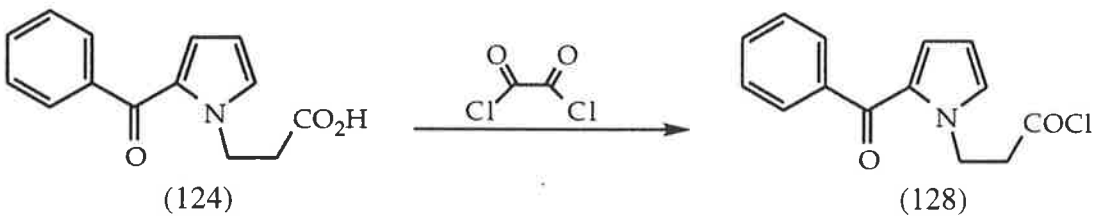


Scheme 82

It is known[90] that certain acids, polyphosphoric acid included, have the ability to rearrange α-carbonyl groups to the β position in these types of systems. Thus the two compounds obtained are presumed to be the respective β-benzoyl isomers (125) and (126). The isomer (127) was also obtained when the reaction time was increased to 4.5 hours (Scheme 82). These compounds are unstable and could not be characterized properly.

When the reaction was carried out at 150°C the ^{1}H NMR spectrum of the crude product material showed resonances due to the desired cyclized material (106), these were however, only present in the minutest amount. A lower temperature of 60°C and a longer reaction time of 18 hours failed to give any of the diketone (106). As the rearrangement occurs with such ease these conditions were no longer investigated.

The next means of cyclization that was attempted was to form the acid chloride (128) (Scheme 83) and to ionise this, to form the oxonium ion via interaction with a Lewis acid and see if cyclization would take place.

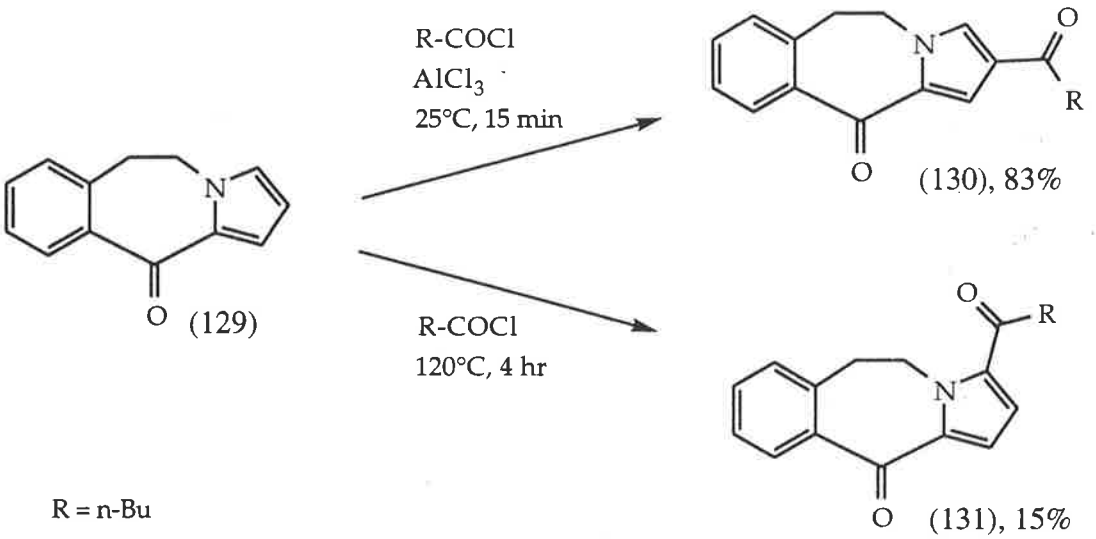


Scheme 83

Girard[91] has acylated the compound (129) (Scheme 84) which is similar to the intended acid chloride (128) in functionality. In the presence of aluminium trichloride β-substitution predominated to give the acylated product (130). Thermal conditions alone also resulted in acylation to give the α-acylated pyrrole (131).

Given the steric constraints of the acid chloride (128) the α-position would be the exclusive site of attack on the pyrrole ring despite electronic factors, if the acylation on this compound does proceed.

Other acylations of deacivated pyrrole compounds have been performed by Kakushima[92] and Wijesekera[93] with use of the Lewis acids aluminium trichloride, boron trifluoride etherate and stannic(IV) chloride.



Scheme 84

The acid chloride (128) was prepared by reaction with oxalyl choride (Scheme 83) and was identified as such by absorptions in the IR spectrum at 1790 and 1630 cm^{-1} due to the carbonyls of the acid chloride and ketone respectively. The ^1H NMR spectrum was similar to that of the nitrile.

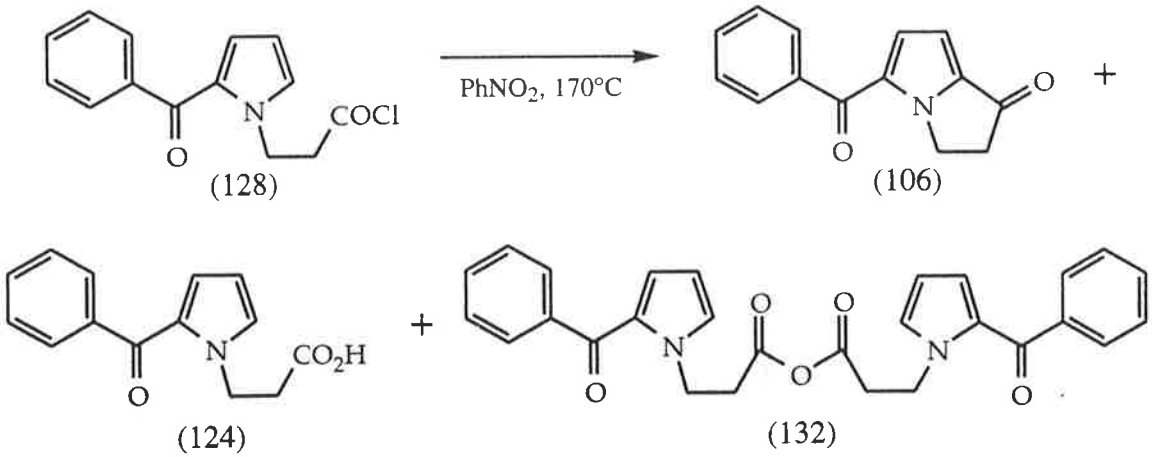
The acid chloride (128) was allowed to react with aluminium trichloride[91] under reflux in chloroform for 1.25 hr. The ^1H NMR spectrum of the crude product mixture showed resonances of small area (<5%) which correspond to the desired diketone (106), thus: triplets at δ 3.15 and 4.76 due to the methylene protons and doublets at δ 6.73 and 7.00 due to the

pyrrole protons, the remainder of the mixture was the carboxylic acid (124) and another compound that remained unidentified.

The reaction was repeated with 18 hr reflux, the ^{1}H NMR spectrum of the crude material showed the presence of the desired compound (106). However, a larger amount of decomposition material was present and acid (124) was not evident.

The conditions were modified to use fourteen-fold excess of aluminium trichloride and nitromethane, which is able to solvate Lewis acids,[92] and a reaction time of 30 minutes at room temperature. These conditions caused some decomposition but the acid (124), from hydrolyis of the acid chloride, was the major material obtained. Neither tin tetrachloride[93] nor boron trifluoride etherate[92] were more effective as a means to catalyse the cyclization.

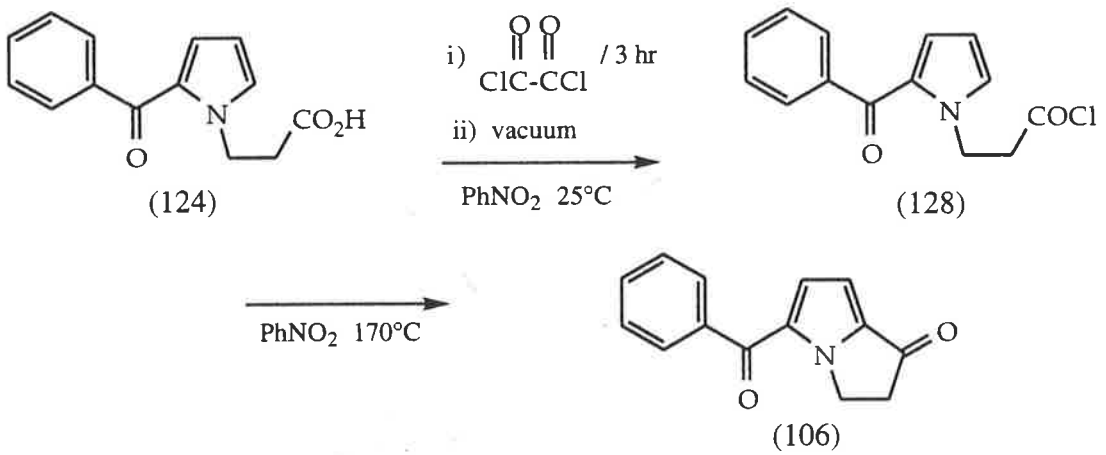
An attempt was now made to use thermal conditions alone,[91] in an appropriate solvent to effect the cyclization. The acid chloride was heated for 18 hr at 170°C in anhydrous nitrobenzene (Scheme 85). Work-up was achieved by removal of nitrobenzene (bp 210°C) under high vacuum. The residue was analysed by ^{1}H NMR spectroscopy which showed resonances due to three compounds; very little decomposition was evident. The desired material (106) was shown to be present in approximately 15%. Resonances that were later confirmed to be due to the anhydride (132) when it was obtained pure in a separate reaction (p95-96) were also present in about 15% area: triplets at δ 3.09 and 4.65 were assigned to the methylene protons and double doublets at δ 6.15, 6.77 and 7.09 due to the pyrrole protons. The aromatic region resonated between δ 7.44-7.77 (the IR spectrum of the pure anhydride (132) showed absorptions at 1820 and 1730 cm^{-1} due to anhydride and 1630 cm^{-1} due to the ketone). The balance of the area of peaks were due to the acid (124). No peaks due to the acid chloride were present. It thus appears that water entered the reaction at some stage which would have occurred if the reaction solvent was incompletely anhydrous to cause some deactivation of acid chloride (128). The acid chloride which remains either reacts with the carboxylic acid to form the anhydride, as approximately 7.5% did, or cyclizing, as *ca.* 15% did.



Scheme 85

Since the reaction was performed on 0.19 mmol of acid chloride (128), it requires a total of only 3 mg of water to enter either through the 20 ml of nitrobenzene solvent used (which is extremely hygroscopic) or at some other stage during the course of the reaction. Thus a method was needed which excludes water in a more rigorous manner.

This was attempted by formation of the acid chloride in nitrobenzene (Scheme 86). Formation of the acid chloride (128) *in situ* would eliminate transfer of reaction solvent and hence there would be less opportunity for water to enter the reaction mixture. Oxalyl chloride is a very effective drying agent that forms only gaseous products from reaction with water, it would thus be used, not only to form the acid chloride (128) but to give anhydrous nitrobenzene. It was thus presumed that after removal of excess oxalyl chloride under high vacuum, the acid chloride (128) in nitrobenzene solution would be strictly anhydrous and as such (128) could be converted completely to the cyclized product at the temperature of 170°C.



Scheme 86: proposed synthetic route

It was however found that after this solution had been heated at 170°C for 18 hours that a larger amount of black coloured polymeric material had formed than could be accounted for by the amount of the pyrrole compound used, which was determined by visual inspection, and is most likely due to reaction of nitrobenzene with oxalyl chloride. The ^{1}H NMR spectrum showed no sign of the desired diketone. Modified conditions were equally unsuccessful.

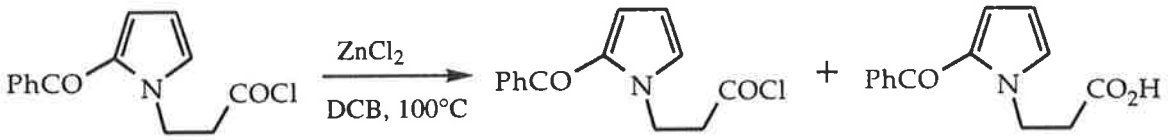
It was thus decided to again prepare the acid chloride in benzene, to remove solvent and excess reagent, and add and heat in dry nitrobenzene. Anhydrous nitrobenzene was prepared via a more rigorous process–heated over phosphorous pentoxide followed by distillation from this drying agent under partial vacuum and stored over activated silica gel. Other changes included the concentration of the acid chloride (128) in nitrobenzene as ten times greater than previously and that the mixtue was heated at 145°C for 18 hours, under dry conditions. The reaction was thus carried out, solvent removed under high vacuum with protection from moisture, and the ^{1}H NMR spectrum of the crude reaction mixture obtained. This showed the clean formation of the anhydride (132), as the only pyrrolic product, which had virtually an identical ^{1}H NMR spectrum as that of the acid (124) except for the resonance due to the methylene α to the carboxylate which was 0.10 ppm further downfield. The compound was confirmed to be the anhydride by IR spectroscopy which showed absorption at 1820 and 1730 cm^{-1}; absorption also occurred at 1630 cm^{-1} due to the ketone. As such it is apparent that at least 1.5 mg of water was present in the reaction system.

As nitrobenzene was insufficiently anhydrous, a different solvent was used which is less reactive so that the acid chloride could be formed *in situ*. The solvent *o*-dichlorobenzene was tried for this purpose; thus oxalyl chloride was added to a solution of the acid (124) in dichlorobenzene and this mixture was stirred at room temperature for 2.5 hr. The mixture was placed under high vacuum for 10 minutes and subsequently heated at 170°C for 18 hr before the solvent was removed under high vacuum. Analysis of the ^{1}H NMR spectrum of the crude product material indicated that no cyclization had taken place and that water had entered the reaction at some stage, as the anhydride (132) had formed. The acid chloride had been completely destroyed–thus it cannot be concluded that the acid chloride will, inherently <u>not form</u> the cyclized product under these conditions. The presence of the acid chloride (128) in

the product mixture would otherwise indicate this, as there was no indication of the cyclized compound (106).

It could be that dichlorobenzene is not able to ionise the carbon-chlorine bond sufficiently, as nitrobenzene appeared to have done, in which case another solvent may be more appropriate or a Lewis acid could be used to properly activate the group.

The latter option was attempted with use of zinc chloride as the Lewis acid (Scheme 87). An anhydrous solution of the acid chloride (128) in dichlorobenzene was prepared as above. The zinc-salt was brought to a completely anhydrous state under the conditions of 200°C/0.02 T inside a 'gooch-tube', which was part of the fully assembled system. This means that no atmospheric moisture could condense on the extremely hygroscopic zinc salt in transfer. Also, excess oxalyl chloride reagent evaporated during this time under high vacuum. The system was released to nitrogen gas, the zinc-salt added and the mixture heated at 100°C for 18 hr. Work-up was achieved by application of high vacuum to the reaction mixture, still at 100°C, to evaporate the solvent. The soluble part of the residue was taken up in d-chloroform and filtered. The ^{1}H NMR spectrum of this solution indicated that the acid chloride (128) was the major pyrrolic component of the product mixture, a small amount of the acid (124) was indicated. There was no indication of cyclization. From this it can be concluded that the creation and maintainance of anhydrous conditions was successful and that cyclization does not occur under these conditions.



(128) (128) (124)

Scheme 87

This procedure was repeated at the higher temperature of 130°C for 18 h, with the change of the use of an aqueous work-up as it was now known that water can be excluded during the reaction, ~~This~~ and gave a crude yield of 22% (86 mg). The ^{1}H NMR spectrum of ~~which~~ this product indicated that it was mostly the required cyclized product (106) and by-and-large the only pyrrolic product. The remainder of the material had polymerised and was insoluble in the extraction solvent. The

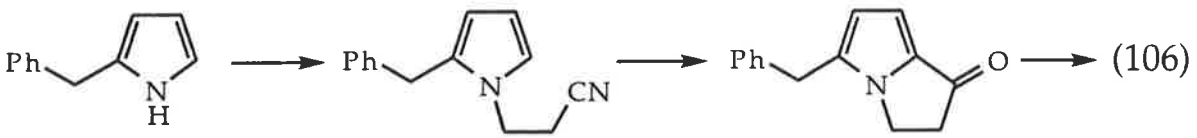
crude diketone (106) was chromatographed with dichloromethane/hexane on silica to give the pure material, the ^{1}H NMR spectrum of which shows the two methylenes to appear at δ 3.15 and δ 4.74 as triplets/double doublets–the three peaks are close to equal height; two 1H pyrrolic resonances appear at δ 6.73 and δ 7.00 as doublets; and the phenyl protons occur as a multiplet between δ 7.48-7.85, which is in agreement with the data reported.[79] The IR spectrum shows absorption at 1715 and 1620 cm^{-1} due to the two carbonyl groups.

Diketone (106) is expected to be more stable than acid chloride (128) so hence a shorter reaction time is unlikely to lead to a greater yield and this was confirmed experimentally.

Magnesium bromide was found to be no more effective as a catalyst than zinc chloride.

These conditions were not efficient enough to form the diketone (106) in workable quantities and so another method was sought.

It was considered that ~~complete removal~~ conversion of the carbonyl to the reduced product (134) (Scheme 88) would give electronic similarity to the cyanoethyl pyrrole (113), which had been successfully cyclized with use of boron trifluoride etherate in a hydrogen chloride saturated ether solution (p84). A synthetic route that could be trialed involves the reduction of 2-benzoylpyrrole to the benzyl derivative (133), which could then be cyanoethylated to form (134). The cyclization should proceed smoothly to give (135) which, it was presumed would undergo oxidation to give diketone (106).

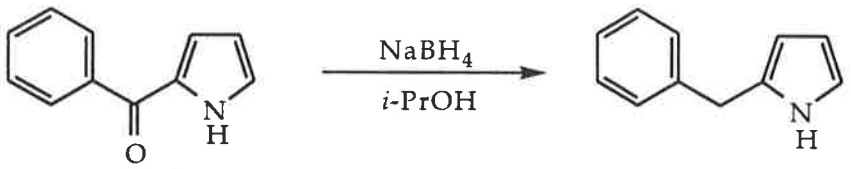


(133) (134) (135)

Scheme 88

Following the procedure of Muchowski[94], 2-benzoylpyrrole was reduced with sodium borohydride in refluxing *iso*-propanol (Scheme 89). The reaction was monitored by analysis of aliquots of reaction mixture as the reduction was not facile. Work-up was by addition of water, removal of the propyl alcohol under reduced pressure, addition of dichloromethane and washing several times with water, to remove traces of propanol. The ^{1}H NMR spectrum of

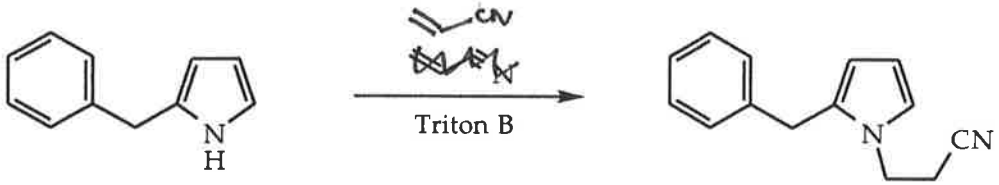
the recovered crude material showed that the reaction had gone to completion: the differences were a 2H singlet at δ 3.85 due to methylene, and the phenyl ring protons now resonated between the narrower range of δ 7.12-7.33.



(104) (133)

Scheme 89

The crude benzylpyrrole was then cyanoethylated to give (134) (Scheme 90), by the procedure of Patterson[82] which is to stir in dioxane solvent with a catalytic amount of Triton B. The ^{1}H NMR spectrum of the crude material showed the product (134) was by-and-large the only pyrrolic compound with many much smaller peaks.

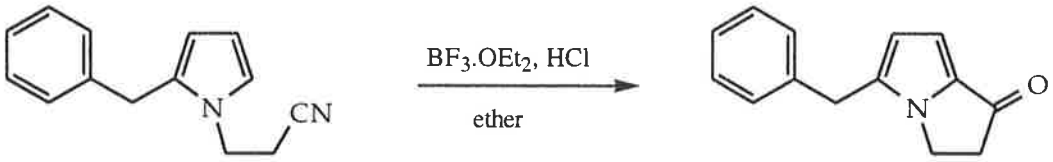


(133) (134)

Scheme 90

Purification was carried out at this stage so as to have well defined conditions in the cyclization reaction, although the pyrrole ring is not stabilized by an electron withdrawing group. The compound was distilled at 135°C/0.05 T to give the nitrile as a yellow oil which later crystallized, in an overall yield of 49%. The ^{1}H NMR spectrum indicated relatively high purity: two triplets due to the methylene groups at δ 2.24 and 3.98; the benzylic methylene protons resonate at δ 3.96; the three pyrrolic protons resonate at δ 6.00, 6.14 and 6.65; and the phenyl protons occur at δ 7.14-7.32. Since the isolation of the crude product mixture is efficient the material was lost in distillation and this was, of course, shown by the polymer residue in the distillation flask.

The cyclization was carried out as in the previously successful case of the non-benzoylated material (113), thus the nitrile (105) was stirred for 26 h in a hydrogen chloride saturated ether solution with boron trifluoride as co-catalyst (Scheme 91). Following removal of the acid catalysts and solvent, the residue was hydrolysed in an aqueous solution of sodium acetate. The usual extraction procedure gave a quantitative yield of what ^{1}H NMR spectroscopy indicated was cyclized material (135) as seen by the now two pyrrolic signals at δ 6.30 and 6.69 which are now seen as doublets. The remainder of the spectrum was similar to that of the nitrile (134). The IR spectrum showed strong absorption at 1700 cm^{-1} which is due to the diketone.



(134) (135)

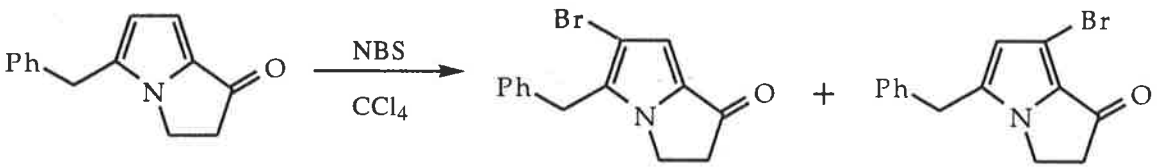
Scheme 91

The purity, as judged by the ^{1}H NMR spectrum was no less than that of the starting material which was high, however it was decided to purify by squat chromatography which yielded the meager amount of 50% of the material that was placed on the column and ^{1}H NMR spectroscopy of this material showed no increase in purity. The, now coloured, column was washed with ethyl acetate, which eluted a mixture of pyrrolic compounds none of which could be identifed. This instability was unexpected as the pyrrole ring is conjugated to the electron withdrawing, and hence stabilizing carbonyl functional group.

Oxidation of the doubly benzylic methylene group would give the required compound (106). Dolby[95] has shown that alkyl pyrroles can be oxidized to ketones by sodium metaperiodate. Thus with use of the co-solvent system of dichloromethane and water the active methylene was attempted to be oxidized with periodate. The compound, however, remained unchanged as indicated by TLC analysis of the reaction mixture which had been stirred vigorously at room temperature for 18 hr.

It was suggested[96] that the benzyl position of (135) be brominated, which would allow greater ease of oxidation. It was believed that competitive bromination at the position α to the carbonyl could be a problem.

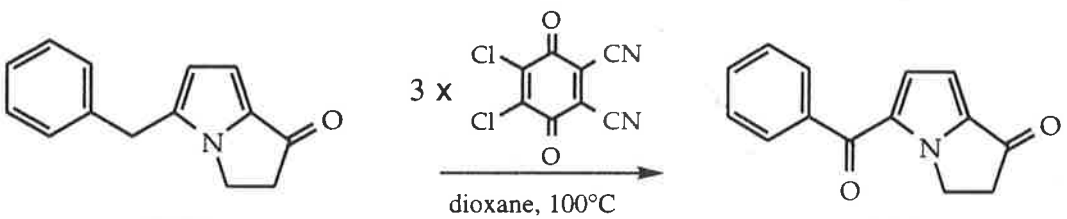
The benzyl pyrrole (135) was allowed to react with *N*-bromosuccinimide in carbon tetrachloride at reflux and was signalled to have formed a bromo compound by the formation of the less dense succinimide which floats on the reaction solvent after the reagent has liberated its bromine atom. Filtration of the reaction mixture followed by evaporation of the solvent gave the product mixture in 94% yield. ^{1}H NMR spectroscopy indicated one major and one minor product (Scheme 92). The types of resonances were identical to those of the starting material, apart from the pyrrolic signals which had now been reduced to one singlet at δ 6.77 ppm. Jones[97] states that bromination occurs readily on the pyrrole ring, which accounts for the singlet resonance. Thus this product is likely to be the 6-brominated compound (136). The minor product also shows a singlet resonance in the pyrrole region of the spectrum at δ 6.27 and is likely to be the isomer with the bromine in the 7 position (137). These compounds were too unstable to allow further purification by chromatography.



(135) (136) (137)

Scheme 92

Rao[98] has used 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to oxidize the benzylic position of electron rich arene rings. This method of oxidation was examined with three equivalents of DDQ in dioxane at reflux (Scheme 93).



(135) (106)

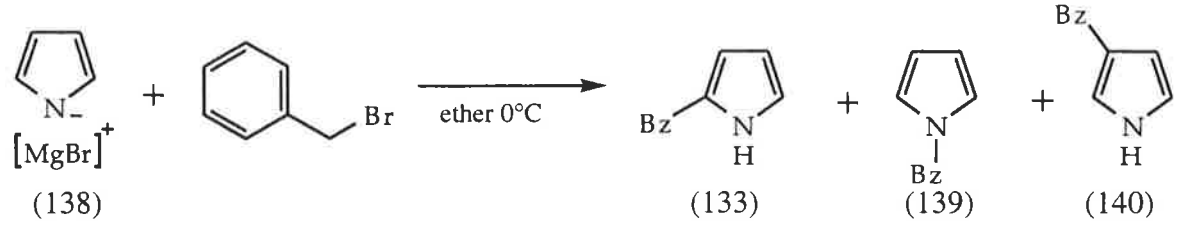
Scheme 93

The product mixture was isolated by filtration from excess DDQ and its reduction product followed by removal of the solvent. This was, however, not fully successful as the hydroquinone, dioxane solvent and pyrrolic material form an intimate mixture. The ^{1}H NMR spectrum of the residue indicated complete and relatively clean conversion to the diketone (106). Dioxane and other material caused absorbtion between δ 3.3 and 4.3. This reaction was performed on 20 mg scale and no yield was measured.

Problems were encountered when this reaction was repeated on a larger scale (up to 4 g). The reaction was refluxed for 6.5 hours, the hydroquinone filtered off and dioxane evaporated under reduced pressure to give the product material which was the black colour expected for DDQ oxidations. ^{1}H NMR spectroscopy showed a large peak at δ 3.73 due to dioxane. Dioxane was removed as an azeotrope with ethyl acetate, however now this solvent was trapped in the crude viscous material. Squat chromatography was unsuccessful as the mixture still contained too much hydroquinone and quinone. A low yield of pure (106) was eventually obtained.

Due to the large amount of time and effort invested to reach this stage along this synthetic route it was considered desirable to further investigate this oxidation reaction, which seemed close to being worked out, to discover a method to procure the diketone (106) efficiently. It was realised that this may not prove wise and other routes were investigated concurrently. These will be discussed later in this chapter.

A more efficient route to obtain α-benzylpyrrole was to attach the benzyl group directly to the α position of pyrrole (rather than benzoylation followed by reduction). Vander Werf[99] has benzylated pyrrole to give (133) in 31% yield (Scheme 94). An ion with small radius, such as Mg^{2+}, gives predominantly the α-carbon substituted product, as the ion binds strongly to nitrogen to give the transition state I (Figure 25), while an ion that binds less strongly allows the electrophile to come close to the nitrogen centre (II). The β isomer (140) was not mentioned by Vander Werf.



(138) (133) (139) (140)

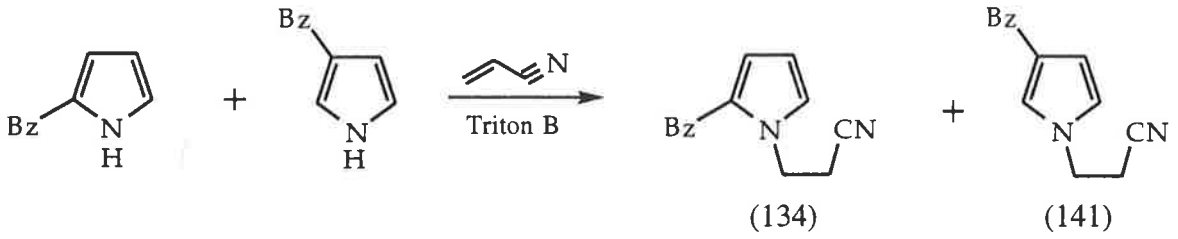
Scheme 94

Figure 25

Thus pyrrole magnesium bromide (138) was prepared from reaction of ethyl magnesium bromide with pyrrole. This was then allowed to react with benzyl bromide at 0°C, followed by work-up with ammonium chloride. The residue was distilled, first to remove excess pyrrole, followed by the products which distilled under high vacuum. The benzylpyrroles distilled at 140°C/0.02 T to give a mixture of the α and β isomers (133) and (140) in a yield of 30% and an approximate ratio of 2/1 as seen by the ratio of the heights of the peaks in the ^{1}H NMR spectrum. The ^{1}H NMR spectrum of the β isomer (140) is assigned as follows: a singlet resonance at δ 3.84 due to the benzylic methylene protons; three double doublets at δ 6.07, 6.50 and 6.69. The aromatic protons occur between δ 7.16-7.32 and a broad signal at δ 7.9 is due to the NH. The presence of the *N* substituted isomer (139) was not indicated in the ^{1}H NMR spectrum of the distilled mixture as there were no doublet resonances in the pyrrolic region. The low yield was due, in part to polymerisation which was caused by distillation conditions that were too vigorous with a small presence of Lewis acidic magnesium cations.

A lower temperature may allow the transition state configuration I (Figure 25) to be held more securely and hence give preferential α substitution. This was not tested.

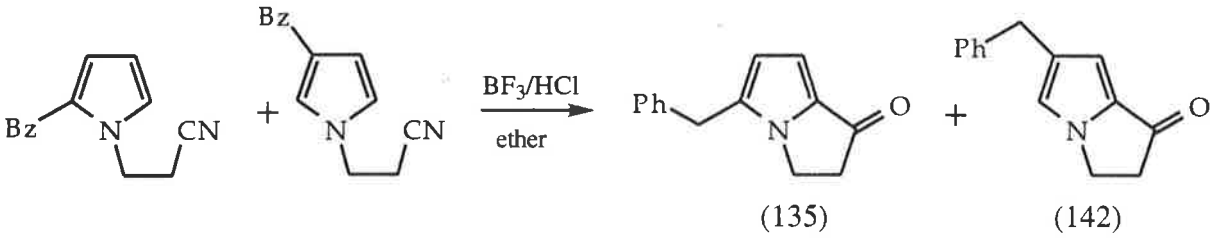
This mixture of α and β isomers was alkylated on nitrogen with acrylonitrile as described previously (p83) to give the mixture of isomers (134) and (141) quantitatively and cleanly (Scheme 95).



(134) (141)

Scheme 95

This mixture was used directly in the next step which was electrophilic aromatic cyclization and was carried out as previously described (p84). This gave the expected mixture of isomers (135) and (142) (Scheme 96). The resonances of the β isomer (142) can be identified in the ^{1}H NMR spectrum of the mixture: the methylene groups occur as triplets at δ 3.01 and 4.18; the benzylic methylene resonates at δ 4.09; the two pyrrolic protons occur as narrow (2.3 Hz) doublets at δ 6.32 and 6.89; and the phenyl ring occurs between δ 7.15-7.35. The α-isomer (135) has been described previously (p100)



(135) (142)

Scheme 96

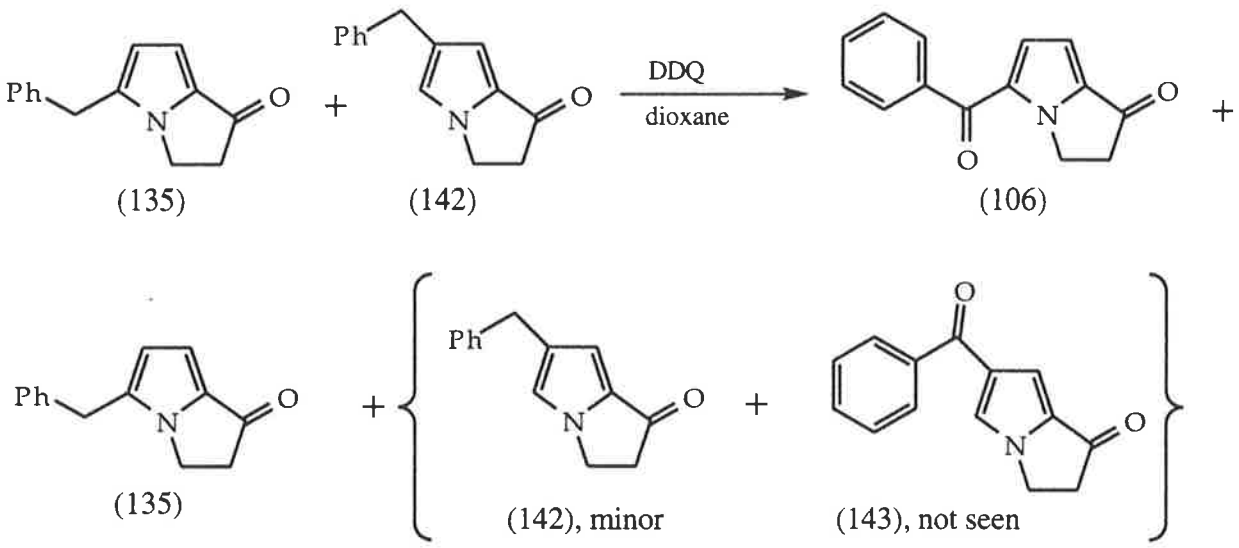
A new set of conditions discovered by Harvey[100] for the DDQ oxidation of benzylic methylene groups uses the solvent system acetic acid/water, which reportedly gives higher yields. Similar conditions were applied to the mixture of isomers (135), (142) above, which was reflux in acetic acid/water (80:20) for 3 hours with 3 equivalents of DDQ. An aliquot was worked up, which showed that no reaction had taken place. Continued reflux was ineffective and only starting mixture was recovered. These conditions are very simple and it was surprising that not even a small amount of the diketone formed.

It was decided to attempt to further optimise the conditions of Rao[98] (p101).

Turner[101] has discovered that the carbonyl oxygen in the oxidation product is derived from water.

To be certain of the reaction conditions, dioxane was purified by fractional distillation from lithium aluminium hydride–to be free from acetals that may consume DDQ oxidant, and also from water. Then, to purified anhydrous dioxane was added a known amount of water (2%) and this used as the reaction solvent.

The mixture of isomers (135), (142) was placed under reflux for 24 h with 3 equivalents of DDQ. Work-up was by removal of dioxane under reduced pressure, the residue was redissolved in dichloromethane before the spent reagent, the hydroquinone–a phenol–was washed out with aqueous base. This work-up was more efficient than that used by Rao which rather involves filtration of the reaction mixture to remove the hydroquinone and quinone (which are relatively insoluble in dioxane) followed by chromatography. This reaction did not go to completion as seen by the ^{1}H NMR spectrum of the crude material, although it proceeded further than reactions performed with unpurified dioxane, to give the expected diketone (106) (Scheme 97).



Scheme 97

The ^{1}H NMR spectum showed a surprising result–the β isomer appears to be unstable under the conditions of the reaction–no peaks were apparent that could be assigned to the β-benzoyl

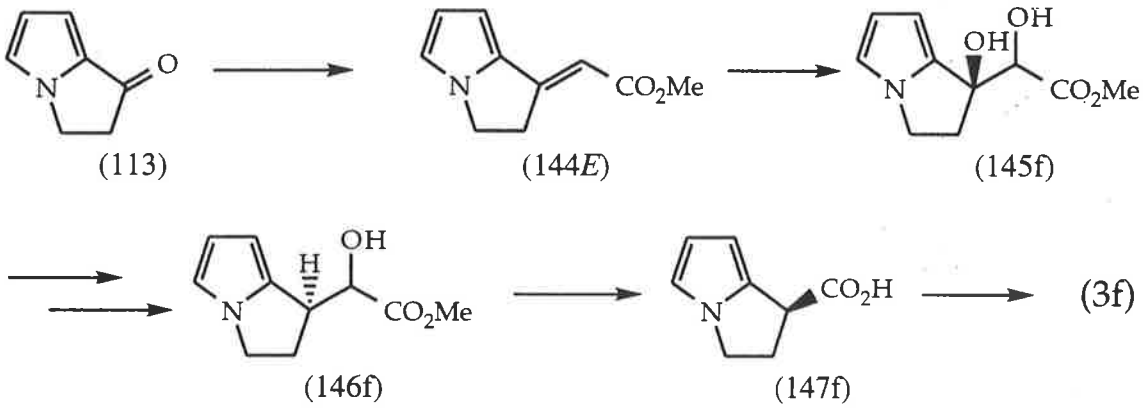
diketone (143), while the β-benzyl ketone (142) was only present in small amounts. A possible reason for this is oxidative cleavage of carbon-carbon bonds to give the carboxylic acid functional group. If formed, these acids would be washed out with aqueous base in the work-up. This would also account for the reaction not going to completion, as DDQ is used up in this side reaction. This was not investigated as this synthetic scheme was discontinued due to time limitations.

The work-up conditions used above were still far from optimal due to practical difficulties–the organic and aqueous phases were the same (black) colour–and overall the recovery of product mixture for these reactions was low, *ca.* 25%.

Due to the difficulty caused by the large amount of hydroquinone and quinone that must be removed in the work-up of these reactions, a reaction was performed on the mixture of isomers (135), (142) which uses only 2 equivalents of DDQ oxidant. It was considerd that this should be sufficient although Rao and Harvey both used 3 equivalents to effect the oxidation of the benzylic methylene groups of their compounds. This reaction, run in 2% aqueous purified dioxane as previously, however, returned only starting material.

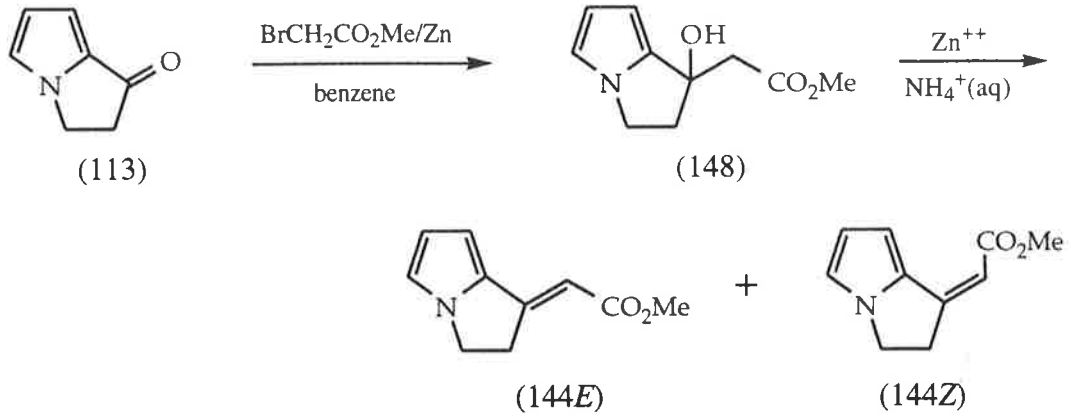
An alternative approach to the synthesis of optically active ketorolac was i) to leave the benzoyl group off initially, ii) establish the pyrrolo-pyrrole ring system with stereogenic centre and iii) attach the benzoyl group as the last step.

Following these ideas (Scheme 98), the first step was to attach a carbon chain at the 1-position (keto) of the pyrrolo-pyrrole (113). The ketone (113) is a vinylogous amide and as such the carbonyl is less susceptible to nucleophilic attack. A reagent will have to be found that is sufficiently nucleophilic. The Reformatsky reaction[102] and the lithium salt of ethyl acetate[103] are two possibilities, to give the addition product (144). This could then give the optically active diol (145f) via the Sharpless AD. Stereoselective reduction of the benzylic C-O bond, either directly or via the corresponding epoxide gives the alcohol (146f) which can be oxidized to the pyrrolo-pyrrole carboxylic acid (147f). The benzoyl group can then be attached[104] to give ketorolac (3f).



Scheme 98

The Reformatsky reaction was carried out by addition of a mixture of the ketone (113) and methyl bromoacetate in benzene to activated zinc dust followed by reflux for 18 hr. The zinc had compacted by the morning and as starting material remained, fresh zinc dust was added and reflux continued. The reaction was worked up by addition of ammonium chloride solution and the resultant mixture allowed to stir for 1 h. This gave the mixture of esters (144*E*) and (144*Z*) (Scheme 99).



(113) (148) (144*E*) (144*Z*)

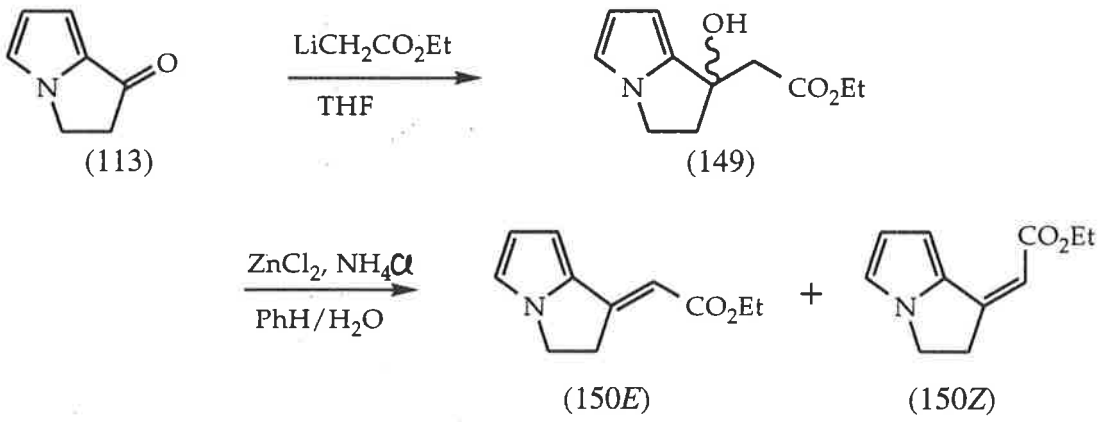
Scheme 99

The dehydration of the intermediate tertiary benzylic alcohol (148) occurred with the use of these mild work-up conditions. Hauser[102] required dilute sulphuric acid to effect the corresponding dehydration for the benzaldehyde addition product. It appears that Zn^{2+} is a sufficiently strong Lewis acid and that the pyrrole nitrogen assists the dehydration by delocalisation onto the benzylic carbon. The ratio of isomers, (144*E*) to (144*Z*) was 5.2/1 as shown by ^{1}H NMR spectroscopic analysis. It is assumed that the thermodynamically favoured *E* isomer is the major isomer, although this was not proved. The methyl of the isomer (144*E*) resonates at δ 3.70, the two methylene groups occur at δ 3.65 and 4.10 as triplets. The former shows further fine coupling to the alkene hydrogen which resonates as a triplet at δ 5.98. The pyrrolic hydrogens are not distinct, due to overlap and occur at δ 6.37, 6.40 and 6.85. The mixture of isomers was, however, not separable by chromatography and the reaction was also not very reproducible due to problems with the zinc dust reagent which tends to coagulate and become coated with organic material. Activated[105] zinc wool was not compacted, however organic material did still coat the surface of zinc and again starting material was often a major component of the recovered product mixture.

Another method to obtain the αβ-unsaturated ester is via lithio ethyl acetate following the general procedure of Rathke.[103] The reagent lithio ethyl acetate was prepared at -78°C from ethyl acetate and lithium diisopropylamide. The ketone (113), as a solid, was added and the reaction mixture was stirred for 20 min (Scheme 100). The reaction was worked up with ammonium chloride solution to give the crude product mixture which was analysed by ^{1}H

NMR spectroscopy. This indicated the presence of a single pyrrolic product, as the aromatic region was very clean and showed 3 double doublets. The rest of the spectrum was more complicated due to the diastereotopic methylene groups.

As the methyl analogue (148) of this compound (149) has been dehydrated during the work-up conditions of the Reformatsky reaction, similar conditions were applied to (149). Thus the alcohol (149) was dissolved in benzene/ammonium chloride solution and zinc chloride added. The mixture was stirred vigorously for 2 days before the product mixture was isolated. The ^{1}H NMR spectrum of the crude material showed that partial dehydration had taken place to give the αβ-unsaturated esters*,[106] (150*E*) and (150*Z*) in an approximate ratio of 1. Conditions should be found to allow equilibration between the *E* and *Z* isomers, however results in another area were proving more fruitful (described below) and so this synthetic route was discontinued at this stage.



(113) (149) (150*E*) (150*Z*)

Scheme 100

Another approach to substitute an alkene functional group in place of the ketone is to form the exocyclic methylene (151) either via the Peterson olefination[107] or the Wittig reaction (Scheme 101). This alkene (151) would be more reactive to the Lewis acidic asymmetric dihydroxylation osmium catalyst, than the ester derivative (144). It also circumvents the problem seen above, of the formation of diastereomers that have to be separated. Thereafter the reactivities of the compounds are similar to those of the ester derivative sequence and hence it is expected that similar reactions could be used to obtain ketorolac (3f).

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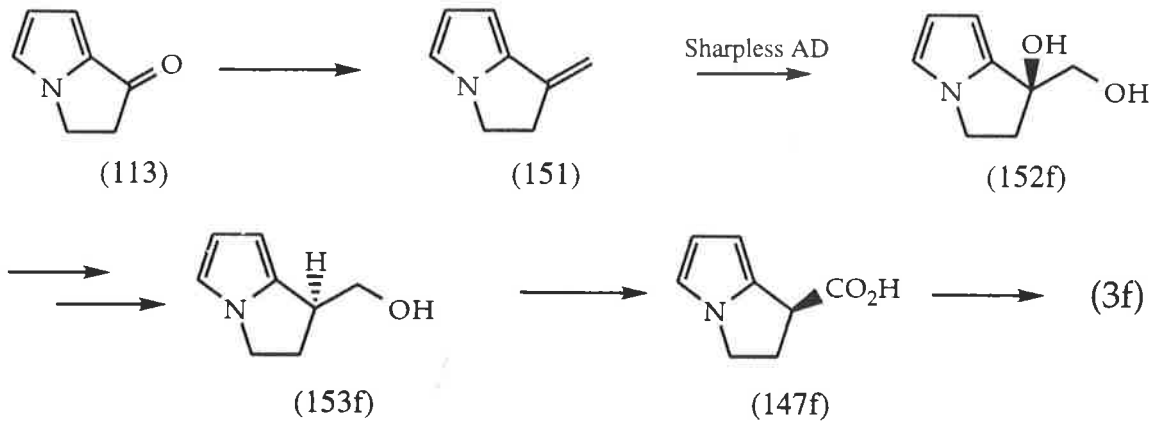
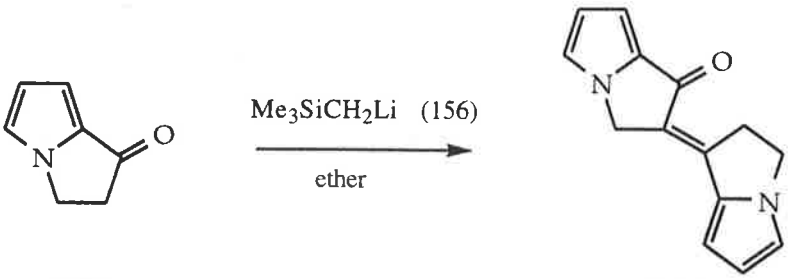
* A mixture of these esters has previously been obtained in this group via the Reformatsky reaction.



(113) (151) (152f) (153f) (147f)

Scheme 101

The olefin (151) formation was attempted first following the procedure by Peterson[107] who has performed this reaction on benzylic and aliphatic ketones, that were more reactive than the pyrrole system (113). The base *sec*-butyllithium was used to generate the silyl nucleophile (155) from tetramethylsilane (TMS). This reaction was performed at -10°C to keep TMS from evaporating. The ketone (113) was added at this temperature and the reaction mixture kept at 0°C for 18 hr. The product was chromatographed to remove unreacted starting material (10% triethylamine/dichloromethane/hexane) before it was identified as the aldol dimer (154) (Scheme 102).



(113) (154)

Scheme 102

The infra red spectrum of (154) shows absorbtion at 1650 cm^{-1} due to carbonyl; at 1600 cm^{-1} due to alkene and at 1530 cm^{-1} due to C-H bending. The ^1H NMR spectrum shows six 1H double doublets which occur at δ 7.01, 6.98, 6.71, 6.48, 6.46 and 6.24. These are due to pyrrolic hydrogens. There are three 2H resonances, one which occurs at δ 4.88 and shows fine coupling of 1.7 Hz, is assigned to the allylic methylene hydrogens of the parent bi-cycle. The other two occur as triplets coupled to each other (6.2 Hz) at δ 4.20 and δ 3.88. The

upfield 2H resonance which shows further fine coupling of 1.7 Hz is assigned to tthe allylic methylene hydrogens of the attached bi-cycle. The downfield signal is assigned to the H3' protons. The ^{13}C NMR shows the presence of 3 aliphatic carbons; the sp^2 hybridized region reveals 6 strong signals due to the C-H carbons and 4 weak signals due to the quaternary carbons; a single signal occurs at δ 180.88 due to the carbonyl. The mass spectrum shows a molecular ion peak at *m/e* 224. It was not discovered whether the *E* or *Z* isomer was formed but the *E* isomer which is shown is less sterically hindered and is likely to form more readily.

Thus it appears trimethylsilylmethyllithium (155) acts as a base in this reaction, rather than a nucleophile, and ~~pulls the enolizable hydrogen off~~ generates the enolate of the ketone (113) which then reacts with another ketone (113) molecule. Peterson has successfully performed olefination reactions with enolizable ketones such as acetone and cyclohexanone by this method.

It was considered possible that butyllithium and TMS were not forming the metalated silane (155) (with butyllithium acting as the base above) as this specific lithio silane was not mentioned by Peterson. This silyl lithium (155) has been formed with use of the metalating agent *N,N,N',N'*-tetramethylethylenediamine (TMEDA) which complexes the lithium cation to leave the butylanion exposed and thus more reactive.[108] The remainder of the procedure was similar to that used above. The same result was obtained, that is, the dimer (154) and starting material.

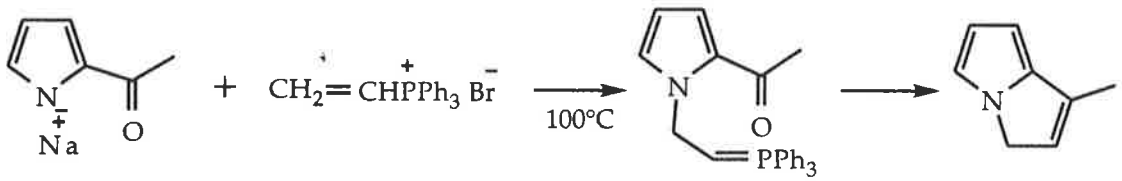
It was considered that the corresponding Grignard reagent (scheme 103) may be more nucleophilic and less basic. However the ^1H NMR spectrum of the crude product mixture showed many pyrrolic compounds.

To see whether reaction conditions had been correctly applied the reaction was performed on *p*-bromoacetophenone. The ^1H NMR spectrum of the product showed the presence of 2 olefinic protons[109] and hence that the conditions had been correctly applied.

(113) (156)

Scheme 103

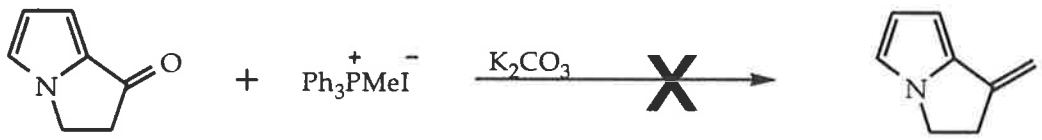
The Wittig reaction with use of the phosphorane was now tried. Schweizer[110] has formed the olefin (159) from the α-carbonyl pyrrole (157) (Scheme 104). This is an intramolecular reaction, once the intermediate (158) is formed *in situ* . The two salts were ground together and fused at 100°C and the product (159) isolated in 43% yield.



(157) (158) (159), 43%

Scheme 104

This procedure was now attempted with use of the ketone (113) and methyltriphenyl-phosphonium iodide (160). Potassium carbonate was used as base as it is known to be a poor catalyst of aldolic condensations.[111] The phosphonium salt (160), the carbonate, and the ketone were powdered separately, mixed together and this mixture placed in the reaction vessel which was a small bomb. The ketone is volatile and evaporated when standard apparatus was used. The reaction was carried out at 150°C by complete submersion in an oil bath for 6 hrs (Scheme 105). Only starting material was recovered as shown by ^{1}H NMR spectroscopy. This was quite unexpected due to the similarity with the reaction carried out by Schweizer. A model reaction to be certain that the experimental conditions were correctly applied was not carried out.

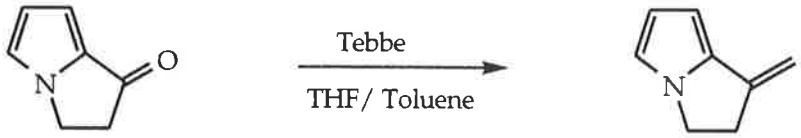


(113) (160) (151)

Scheme 105

The reaction was also carried out with the above reagents with use of dioxane as solvent. Gaset[111] has carried out a number of olefinations with aromatic aldehydes which bear electron-donating groups with use of this solvent with a small amount of water. Similar reaction conditions did not however produce any of the desired material.

The Tebbe reagent[112,113] was used next, following the procedure of Wattansin[114] who has converted *N* acylated indoles and pyrroles to the corresponding exo-methylene compounds. The ketone (113) was reacted with 2 equivalents of the Tebbe reagent in the solvent system of THF/toluene for 2 hours at room temperature (Scheme 106). On completion of the reaction excess reagent was destroyed with methanol and the solution dried with sodium carbonate. Solids were filtered off and the filtrate concentrated under reduced pressure. Chromatography on silica with 15% triethylamine in hexane gave the alkene (151). Residual triethylamine solvent was removed under high vacuum as it was noted that the alkene (151) is very heat sensitive.



(113) (151)

Scheme 106

The next reaction in the sequence is the Sharpless AD, which uses optically active amines in catalytic amounts. It is noted that the presence of an amine in the reaction, other than the correct ligand, such as triethylamine, would result in lower optical purity of the product diol (152f). The alkene (151) was thus purified by chromatography on alumina with dimethyl-amine gas dissolved in dichloromethane (5:95). This amine, as a gas, is much more easily removed before the AD reaction.

The alkene (151) was stabilized by the radical inhibitor di-*tert*-butyl-*p*-cresol and dimethylamine in d-chloroform NMR solutions. The ^{1}H NMR spectrum showed the methylene groups as triplets which occur at δ 3.21 and 4.09, the former signal is the allylic group and shows further coupling to the alkene protons. These olefinic protons occur at δ 4.87 and 5.24, both as triplets. The pyrrolic protons occur as double doublets at δ 6.24, 6.36 and 6.73. The IR spectrum shows the alkene absorption at 1620 cm^{-1}.

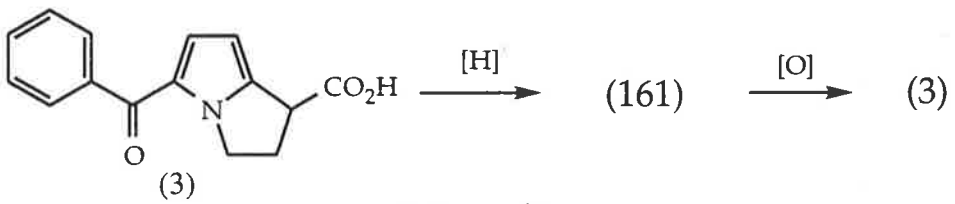
As the Tebbe reagent is expensive, the reaction was attempted with only 1 equivalent, as described by Pine[113] with amides as substrates. Wattansin[114] recommends the use of 2 equivalents to bring the reaction to completion and this was found to be the case as the ketone (113) was only 50% converted to the alkene after the usual reaction time.

The next step was the Sharpless AD[35] reaction. The alkene (151) was freshly prepared for each attempt at this reaction as it was too unstable to store for longer periods. Similar conditions were used for the alkene (151), as were used during the synthesis of naproxen (p62). ^{1}H NMR spectroscopic analysis of the crude product mixture showed many pyrrolic compounds, nothing of which was recognisable as the desired diol (152f).

The formation of the racemic diol (152r) was also attempted according to the general conditions of VanRheenen.[65] The ^{1}H NMR spectrum of the crude material was cleaner than that of the material of the AD reaction, however, again nothing could be identified.

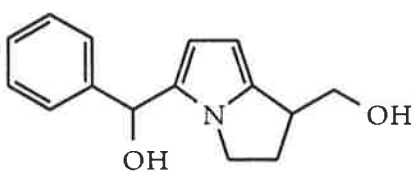
Due to time constraints attempts towards the asymmetric synthesis of ketorolac were discontinued at this stage.

Before the synthetic route was investigated from the start, the last step of the synthetic sequence was investigated by reduction of commerically available ketorolac (3) and re-oxidation of the reduction product (161) (Scheme 107). This was done to see whether the reduction product (161) which was expected to be the pyrrole/alcohol system (162) (Figure 26) and is quite unstable, would stand up to the oxidative conditions necessary for the last step of the synthesis of (*S*)-ketorolac. It was hoped that the expected doubly benzylic hydroxyl, of the reduction product (161), would be rapidly re-oxidized and give stability to the pyrrole system. This particular intermediate (161) may not necessarily be the penultimate compound in the planned reaction sequence of ketorolac (Scheme 69a) so this experimentation is not necessarily conclusive.



(3)

Scheme 107



(162)

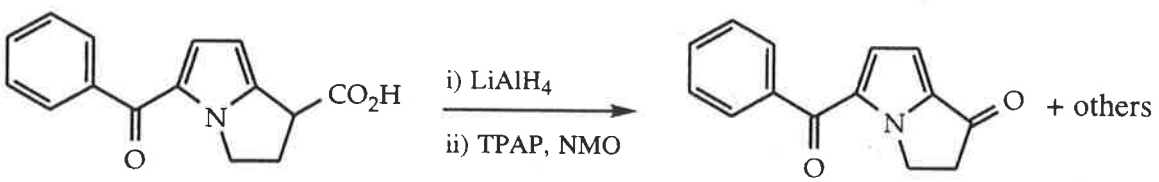
Figure 26

Reduction of ketorolac (3) with lithium aluminium hydride at room temperature gave a single product, as seen by TLC, which could not be conclusively identified by ^{1}H NMR spectroscopy, however the signals due to the phenyl protons were less spread out and two broad signals which could have been due to hydroxyl protons were present, however more signals were present than could be accounted for in terms of the compound (162). The compound was too unstable to be chromatographed on silica.

The re-oxidation was attempted according to the ruthenium tetroxide conditions of Sharpless.[53] The reduction product (161), obtained in 85% yield, was immediately placed under the conditions of sodium metaperiodate in the solvent system of carbon tetrachloride, acetonitrile and water with the catalytst ruthenium tetroxide. The mixture immediately developed a strong red colour, which indicated that polymerization had taken place and this was confirmed 1.25 h later by TLC analysis. The polymerisation was most likely caused by acid–either Brønsted or Lewis. The reaction was also tried with use of periodic acid and sodium carbonate to remove the potential for Brønsted acid catalysed decomposition, however this was not successful. Milder methods of oxidation were sought.

Ley[115] has successfully used *N*-methylmorpholine-*N*-oxide/tetra-n-propylammonium per-ruthenate (TPAP)[116] to oxidize a pyrrole carbinol to a ketone. These conditions are basic and as such, less likely to cause polymerization of sensitive pyrrole compounds.

Reaction of freshly prepared reduction product (161), with TPAP and NMO in acetonitrile (Scheme 108) gave a mixture which ^{1}H NMR spectroscopy indicated contained the diketone (106) as the major component and several other minor compounds which remained unidentified. There was no sign of ketorolac. These conditions are clearly too vigorous and oxidize the benzylic methylene group to the ketone.



(3) (106)

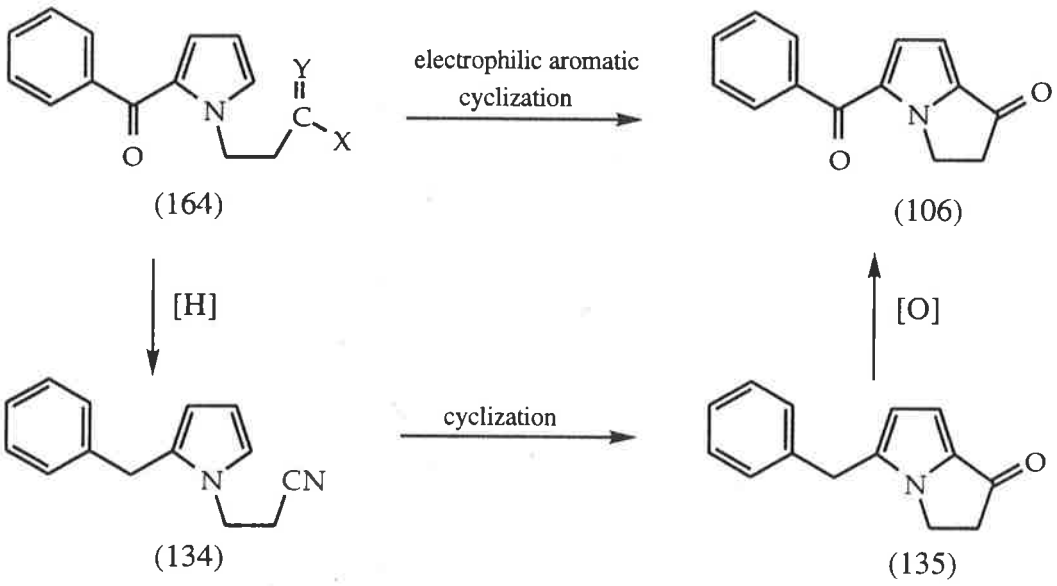
Scheme 108

Carey[117] has reduced ethyl (*E*)-4-(1-propenyl)pyrrole-carboxylate with lithium aluminium hydride and re-oxidized the carbinol pyrrole product to the aldehyde under anhydrous conditions with activated manganese dioxide in 30% yield. When these conditions were used on ketorolac's reduction product (161), the diketone (106) was again the only product identified by ^{1}H NMR spectroscopy.

In conclusion this pyrrole chemistry proved to be very difficult and a large number of negative results were not included. The reactivity of these compounds appears to fall in the areas of the extremes of quite unreactive or extremely reactive–such that polymerisation occurred almost instantly. There was very little middle ground where useful transformations could be carried out.

It was attempted to form the bicyclic benzoylpyrrole (106) (Scheme 109) by closing the second ring via electrophilic aromatic cyclization. Several functional groups (164) were trialed in attempts to polarise the terminal carbon sufficiently to cause reaction with the pyrrole ring. The latter was, however, too electron deficient to react in a facile manner due to the electron withdrawing benzoyl group in conjugation with the pyrrole ring. The diketone was formed under several different reaction conditions, however not in workable quantities.

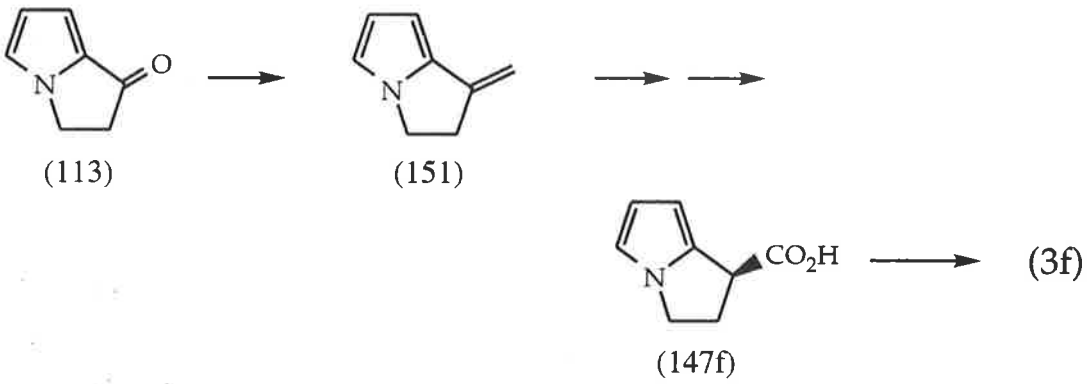
The problem of the inertness of the pyrrole ring to further substitution, was solved by



Scheme 109

removal of the carbonyl to the methylene group of compound (134), which allowed the pyrrolopyrrole (135) to be formed. Re-oxidation of the methylene group gave the diketone (106), however due to time limitations, this route could not be fully worked out.

Another route that was trialed was to set up the pyrrolopyrrole with the carboxylic acid functional group in the correct stereochemistry (147f) and subsequently attach the benzoyl group to give ketorolac. The intermediate compounds here were, however, extremely unstable and difficult to work with.



(113) (151) (147f)

Scheme 110

EXPERIMENTAL

GENERAL

Melting points were determined using a Kofler hot stage apparatus under a Reichert microscope and are uncorrected.

Microanalyses were performed either by the Australian Microanalytical Service, Melbourne, or the University of Otago, Chemistry Department, Dunedin, New Zealand.

Infrared spectra were recorded on a Jasco A-102 spectrometer as nujol mulls of liquid films, or as solutions when indicated. ^{1}H NMR spectra, were obtained at 300.166 MHz, ^{13}C NMR were obtained at 75.5 MHz on the Brüker ACP-300 spectrometer, unless otherwise indicated in which case the spectra were recorded on a Varian Gemini 200. The integration program used for accurate determination of areas was WIN-NMR Brüker-Franzen Analytik GmbH Version: 930405. Chemical shift (δ) values have been quoted in parts per million downfield from tetramethylsilane. Peak multiplicities have been abbreviated to s (singlet); d (doublet); t (triplet); q (quartet) and quint (quintet), m (multiplet).

Electron impact mass spectra were recorded at 70 eV on an AEI 3074 mass spectrometer. Fast atom bombardment mass spectra were recorded on a V.G. ZAB 2HF mass spectrometer.

Optical rotations were measured using a Perkin-Elmer 141MC Polarimeter. Specific rotations ($[\alpha]_D^{20}$) are reported in degrees per decimeter at 20°C and the concentration (c) is given grams per 100 ml in the specified solvent.

Flash chromatography[118] was performed with Merck Kieselgel 60 (230-400 mesh ASTM). Squat chromatography was performed using Merck Kieselgel 60 PF_{254}. Thin layer chromatography (TLC) was performed with Merck DC-Alufolien Kieselgel 60 F254 Art. 5554. TLC plates were visualised either with UV light or by immersion in vanillin dip [prepared by dissolved vanillin (15 g) and concentrated sulphuric acid (3 ml) in absolute ethanol (100 ml)] followed by heating.

All solvents were distilled before use. Anhydrous ether and THF were freshly distilled from sodium/benzophenone. Other anhydrous solvents and reagents were prepared according to standard laboratory procedures.[119] All organic extracts were dried over anhydrous sodium sulphate unless otherwise specified. Hexane refers to the fraction with boiling range 66-69°C.

CHAPTER 1

Ethyl-(E)-3-(4'-bromophenyl)-2-butenoate (66E):

To super dry ethanol (150ml) under nitrogen, was added lithium (0.68 g, 98 mmol, 1.3 equiv.) and the mixture stirred until the lithium had dissolved, whereupon diethylphosphonoacetate (18.6 g, 83 mmol, 1.1 equiv.) was added and the mixture stirred for 5 min. *p*-Bromoacetophenone (15.0 g, 75 mmol, 1 equiv) was added and the reaction mixture was stirred at room temperature for 42 h before it was worked up by addition of saturated ammonium chloride solution. The solvent ethanol, was removed under reduced pressure before the aqueous residue was extracted with dichloromethane. The combined extracts were washed once with water, dried and evaporated under reduced pressure to yield 21.8 g of the crude reaction mixture (yield >100%). ^{1}H NMR analysis showed a diastereotopic ratio *E*/*Z* of 30 based on the vinylic proton. The isomers can be separated by squat chromatography, on elution with hexane to give the pure *E* isomer. ^{1}H NMR: δ 1.31 (t, *J* = 6.8 Hz, $CH_2C\underline{H}_3$), 2.54 (s, CH_3), 4.23 (q, *J* = 6.8 Hz, $C\underline{H}_2CH_3$), 6.11 (s, CH), 7.31-7.49 (AA'BB', Ar). The *Z* isomer was not obtained pure.

3-(4'-Bromophenyl)-2-butene-1-ol (67E):

A stirred suspension of lithium aluminium hydride (3.4 g, 90 mmol, 1.2 equiv), in dry ether (150 ml) was cooled to -78°C. The crude αβ-unsaturated ester mixture (21.8 g) obtained above was added dropwise to the stirred hydride suspension. The reaction mixture was stirred at -78°C for 6 h before it was worked up by dropwise addition of a saturated solution of sodium sulphate until the aluminium salts had completely coagulated.[120] The grey conglomerate was extracted twice with ether and the extracts filtered through celite. The ether was evaporated under reduced pressure before the residue was redissolved in dichloromethane, washed once with water, dried and the solvent evaporated under reduced pressure. The residue was sublimed at 100-110°C/0.1 T to give 14.58 g (64 mmol, 85% based on *p*-bromoacetophenone) of the mixture of isomers as an off-white solid which was

recrystallized three times from a 1:1 mixtue of ether/hexane (20-40 ml), in each case the mixture was cooled to -15°C, to obtain the pure *E* diastereomer, as shown by ^{1}H NMR analysis. This was obtained in a yield of 6.97 g (30.7 mmol, 41% based on ketone) and had a melting point of 58-59°C. ^{1}H NMR: δ 1.79 (s, OH), 2.04 (apparent s, CH_3), 4.34 (d, J = 6.8 Hz, CH_2), 5.95 (tq, J = 6.8, 1.3 Hz, CH), 7.24-7.44 (AA'BB', Ar).

(2RS,3RS)-3-Methyl-3-(4'-bromophenyl)oxiranemethanol (25r):

To a stirred solution of the allylic alcohol (67*E*) (2.81 g, 12.38 mmol) in dichloromethane (30 ml) at 0°C, was added portionwise, *m*-chloroperbenzoic acid[48] (3.04 g, 14.15 mmol, 80%). The mixture was allowed to warm to room temperature and was stirred for 2.5 h before it was worked up by addition of a 10% aqueous solution of sodium hydroxide saturated with sodium chloride to the vigorously stirred reaction mixture until the organic layer cleared. Saturated sodium thiosulphate solution (0.5 ml) was added and the mixture was stirred for 10 min before the layers were separated and the aqueous phase extracted with dichloromethane. The combined organic phases were washed once with 10% sodium hydroxide solution, once with water, dried, and the solvent removed under reduced pressure to give the racemic epoxide (25r) in 94% yield. The crude material was recrystallized from ether/hexane (90:10) to give the epoxide as white needle-like crystals in an overall yield of 62%. Spectral data are identical to those of the optically active epoxide (25f).

(2S,3S)-3-Methyl-3-(4'-bromophenyl)oxiranemethanol (25f):

The epoxidation was carried out according to a general procedure by Sharpless.[26] A dry 500 ml single neck flask fitted with a magnetic stirring bar and septum was charged with of L-(+)-diisopropyl tartrate (0.534 g, 2.28 mmol, 7.5% equiv.) and dry dichloromethane (300 ml). After the mixture was cooled to -20°C, activated, powdered 4Å molecular sieves (2 g), titanium tetraisopropoxide (0.452 ml, 0.432 g, 1.52 mmol, 5% equiv.), and a solution of *tert*-butylhydroperoxide (TBHP) (60.8 mmol, 17 ml, 3.95 M, 2 equiv.) in dichloromethane were added sequentially. The mixture was allowed to stir at -20°C for 1 h before addition of a solution of 3-(*p*-bromophenyl)-2-butene-1-ol (6.9 g, 30.4 mmol, 1 equiv.) in dichloromethane

(20 ml), dropwise, over 5 min. After 4 h at -20°C, the reaction was quenched by addition of a 10% aqueous solution of sodium hydroxide saturated with sodium chloride (2.4 ml). After ether (30 ml) was added, the cold bath was removed and the stirred mixture was allowed to warm to 10°C, whereupon anhydrous magnesium sulphate (2.4 g) and celite (0.3 g) were added, the mixture stirred 15 min, and the filtrate collected through a celite pad. The solvent was removed under reduced pressure to leave a mixture of the crude epoxide and TBHP, the latter of which was removed as an azeotrope with toluene under reduced pressure, to yield an off-white solid which was sublimed at 125°C/0.02 T to obtain 6.30 g (25.9 mmol, 85%) of the *title compound.* This was recrystallized from ether/dichloromethane (75 ml, 30 ml) at -15°C to give white needle crystals (4.22 g, 17.38 mmol, 57% total, >95% ee by ^{1}H NMR analysis outlined below). Mp 124-131°C, $[\alpha]^{20}_D$= 26.5° (c= 1.32 EtOH). ^{1}H NMR: δ 1.68 (s, CH_3), 1.76 (br s, OH), 3.05 (dd, *J* = 6.5, 4.4 Hz, CH), 3.84 (dd, *J* = 12.0, 6.3 Hz, C<u>H</u>H), 3.96, (dd, *J* = 12.0, 4.4 Hz, CH<u>H</u>), 7.19-7.49 (AA'BB', Ar). ^{13}C NMR: δ 17.6, 60.4, 61.2, 66.0, 121.5, 126.8, 131.5, 141.1. $C_{10}H_{11}O_2Br$ requires: C, 49.41; H, 4.56; found: C, 49.20; H, 4.49.

*(2*RS*,3*SR*)-3-Methyl-3-(4'-bromophenyl)oxiranemethyl Acetate (69r)* and
*(2*R*,3*S*)-3-Methyl-3-(4'-bromophenyl)oxiranemethyl Acetate (69f):*

Performed separately with the racemic and optically active material:
A mixture of the epoxy alcohol (25) (16 mg, 0.066 mmol) and acetic anhydride (31 µl, 0.33 mmol, 5 equiv.) in triethylamine (0.5 ml), was stirred for 15 h at room temperature before the crude product was obtained by evaporation of the solvent and excess reagent. This residue was distilled at 80°C/0.03 T to give the pure material. Yields were: 47% for the racemic actate (69r) and 94% for the optically active acetate (69f). ^{1}H NMR: δ 1.69 (s, CH_3), 2.12 (s, $COCH_3$), 3.05 (dd, *J* = 6.4, 4.4 Hz, CH), 4.17 (dd, *J* = 12.2, 6.4 Hz, C<u>H</u>H), 4.43 (dd, *J* = 12.2, 4.4 Hz, CH<u>H</u>), 7.20-7.48 (AA'BB', Ar).

Method of analysis of the optical purity of the asymmetric epoxide (25f):

An appropriate w/w of epoxy acetate (69)/Eu(hfc)$_3$ is close to 1. The following respective amounts of epoxy acetate and Eu(hfc)$_3$ were used: racemic–13.9 mg, 16.4 mg; Optically active–16.4 mg, 19.4 mg in 1-1.5 ml deuterochloroform. ^{1}H NMR spectra were recorded at this stage. *Ca.* 0.25 mole equivalents of water (to the epoxy acetate) was added to both of the NMR solutions: 220 µl, and 260 µl. No peak could be detected at the base of the major resonance of the optically purified material.

3-(4'-Chlorophenyl)-but-2-en-1,2-diol (70):

To a solution of the epoxide (46) (100 mg, 0.504 mmol) in benzene (5 ml) was added titanium tetraisopropoxide (300 µl, 1.01 mmol). The mixture was stirred at room temperature for 15 h before the reaction mixture was diluted with ether and the reaction quenched with 10 ml of a 5% aqueous solution of sulphuric acid and the resultant mixture was stirred for 18 h. The phases were separated and the aqueous phase extracted once with dichloromethane. The combined organic phases were washed once with water, dried and the solvent evaporated under reduced pressure to give the *title compound* in 92% yield (92 mg, 0.46 mmol) which was recrystallized from ether/hexane to give white crystals in a yield of 76% and mp 72-74°C. ^{1}H NMR: δ 2.74 (br s, OH), 3.18 (br s, OH), 3.43 (dd, *J* = 11.4, 7.5 Hz, 1H, H1), 3.65 (dd, *J* = 11.4, 3.0 Hz, 1H, H1), 4.73 (dd, *J* = 7.5, 3.0 Hz, 1H, H2), 5.40 (s, 1H, H4), 5.45 (t, *J* = 0.9 Hz, 1H, H4), 7.26-7.31 (AA'BB', Ar). υ_{max} (nujol): 3380, 1630, 1600 cm^{-1}. Mass spectrum: 200, 198 ($M^{+\cdot}$), 182, 180, 169, 167. $C_{10}H_{11}O_2Cl$ requires: C, 60.44; H, 5.58; found: C, 60.43; H, 5.74.

Trial reactions performed to optimise the yield of *3-(4'-Chlorophenyl)butane-1,2-diol (47):*

Reduction of *(2S,3S)-3-Methyl-3-(4'-bromophenyl)oxiranemethanol (25f):*

Reagents used and results are shown in Table 2 on page 48. To a stirred suspension under dry conditions, formed by brief sonication of 3-(*p*-chlorophenyl)-2,3-epoxy butan-1-ol (1 mmol) in dry solvent (3 ml) was added Ti(O-*i*-Pr)$_4$ (1.1 mmol) and the mixture stirred until the epoxide had completely dissolved. Lithium borohydride was added quickly and the flask was placed under nitrogen. After sonication for 5 min the mixture was stirred vigorously for 1-2

days before addition of dichloromethane and transferral to a 250 ml flask. The reaction was quenched by addition of water and allowed to stand for a few minutes. This mixture was filtered through celite, and the celite cake and filtrate extraced with dichloromethane. The combined extracts were washed once with water, dried and the solvent evaporated under reduced pressure (100 mm Hg). The higher boiling solvents were removed under high vacuum to obtain the mixture of the 1,2-diol (47), 1,3-diol (71) and the alkene-1,2-diol (70). The signals used in ^{1}H NMR analysis were the following: the methine hydrogen at δ 2.73 of the 1,2-diol, the methylene at δ 2.0 of the 1,3-diol, and the vinylic hydrogen at δ 5.43 of the alkene diol (Figure 18).

The reaction which used only 3 equivalents of lithium borohydride gave a small amount of alkene (70) as the sole product, the remainder of the recovered material was epoxide (46).

(2R,3S)-3-(4'-Bromophenyl)-butane-1,2-diol (26f):

Using modified conditions of Dai,[32] a stirred suspension of the epoxide (25f) (1.20 g, 4.94 mmol) in dry xylene (35 ml) was added titanium tetraisopropoxide (1.62 ml, 5.43 mmol, 1.1 equiv.) and the mixture allowed to stir until the epoxide had completely dissolved. Lithium borohydride (1.6 g, 73.4 mmol, 15 equiv) was added quickly to minimise exposure to atmospheric moisture, and the reaction mixture placed under nitrogen. After sonication (5 min), to aid dissolution of the borohydride, the mixture was stirred vigorously for 3 days before it was transferred to a 250 ml flask with use of dichloromethane, quenched by cautious addition of 15% hydrochloric acid solution and allowed to stand for a few minutes to allow the initially precipitated titanium salts to redissolve. The mixture was filtered through celite followed by extraction with dichloromethane. The combined extracts were washed once with water, dried and the solvent evaporated under reduced pressure, xylene was removed under high vacuum, to obtain 1.11 g (92%) of the mixture of diols: the *title compound* (26f), 2-(*p*-bromophenyl)-2-methylpropane-1,3-diol (75) and 3-(*p*-bromophenyl)-but-2-en-1,2-diol (76). ^{1}H NMR analysis showed a respective ratio of 80:16:4 of the three diols. The *title compound* was not obtained pure.

3-(4'-Chlorophenyl)-butan-1,3-diol (71):

To a solution of chloro epoxide (46) (100 mg, 0.5 mmol) in 1 ml of diglyme under dry conditions was added lithium borohydride (87 mg, 4 mmol). The mixture was sonicated for 5 min before it was stirred for 22 h at room temperature. The reaction was worked up by addition of water and the resultant mixture was stirred for 1 h. The mixture was extracted with dichloromethane, the combined organic phases were washed with water, dried and the solvent removed under reduced pressure. The product was isolated from the residual diglyme solution by chromatography as an oil. These conditions are not optimized; the yield was not obtained. ^{1}H NMR: δ 1.51 (s, CH_3), 1.94 (ddd, J = 14.6, 4.9, 3.4 Hz, 1H, H2), 2.05, (ddd, J = 14.6, 8.8, 4.4 Hz, 1H, H2), 3.40 (br s, OH), 3.50 (m (apparent dt), 1H, H1), 3.71 (m, 1H, H1), 4.40 (s, OH), 7.26-7.36 (AA'BB', Ar).

2-(4'-Chlorophenyl)-2-methylpropan-1,3-diol (74):

To a stirred solution of the epoxide (46) (500 mg, 2.52 mmol) in dry dichloromethane (8 ml) at -40 °C and under a nitrogen atmosphere, was added 1-1.5 ml of Me_3SiH (750-1100 mg, 10-15 mmol, 4-6 mol equiv.), which is a gas at room temperature, and boron trifluoride etherate (1.6 ml, 5 mmol, 2 mol equiv.). The reaction was stirred for 10 min before it was worked up by addition of solid potassium carbonate followed by water. The mixture was extracted with dichloromethane, the combined organic phases were dried, and the solvent evaporated under reduced pressure to give the product mixture as a solid which was chromatographed (1:1 ethyl acetate/hexane) to give 190 mg (0.95 mmol, 38%) of the diol (74) in three fractions, the purest of which was recrystallized from ether/hexane in 79% yield, to give crystals of mp 83-85°C. ^{1}H NMR: δ 1.24 (s, CH_3), 2.43 (s, 2H), 3.78 (d, J = 11.1 Hz, 2H, H1, H3), 3.91 (d, J = 11.1 Hz, 2H, H1, H3), 7.30-7.37 (AA'BB', Ar). ^{13}C NMR: δ 20.79 ($\underline{C}H_3$) 44.14 ($\underline{C}$), 69.77 (2C, C1, C3), 128.16 (2C), 128.65 (2C), 132.45, (1C), 141.62, (1C). Mass spectrum: 202, 200 ($M^{+\cdot}$), 171, 169, 154, 152.

Dehydration conditions for the mixture of alcohols:

A solution of the crude mixture obtained above was dissolved in dry redistilled dimethylsuphoxide (20 ml) and heated[53] at 180°C for 2.25 h after which time TLC analysis showed the complete disappearance of the 1,3-diol (75) and the appearance of the allylic alcohol (67*E*). DMSO was removed by distillation initially at 120°C/80 mm and subsequently at 40°C/1 mm. The distillation was, however, stopped prematurely, the weight of the residue (1.5 g) indicated that not all DMSO had been removed. This was to cause problems in later purification steps.

(S)-2-(4'-Bromophenyl)propanoic Acid (50f):

A 100 ml 'bomb' type flask with no ground glass surfaces (to which the volatile ruthenium catalyst tends to adhere) and which contains a magnetic stirring bar was charged with a portion of the mixture of diols (884 mg) obtained in the last step, sodium metaperiodate (3.86 g, 18.1 mmol, 5 mol equiv), ruthenium trichloride (14.2 mg, 0.0722 mmol, 2% equiv) and the bi-phasic solvent system of carbon tetrachloride (8 ml), acetonitrile (8 ml) and water (12 ml). The reaction mixture was stirred for 1.75 h before it was worked up by addition of water and extraction with dichloromethane. The combined organic phases were washed once with water, dried and evaporated under reduced pressure; the residue was redissolved in ether, allowed to stand 15 min to precipitate the ruthenium catalyst, which was filtered off through celite. The filtrate was evaporated to give a light brown solid which ^{1}H NMR anlysis showed contained the *title compound* (50f), *p*-bromobenzoic acid (77) and *p*-bromoacetophenone. Methyl sulphone (^{1}H NMR: δ 2.99) was also present.

Purification of the *title compound*:

Purification of 2-(*p*-bromophenyl)propanoic acid was carried out by use of the slight difference in acid strength between the two carboxylic acids and the neutrality of acetophenone.

To the residue was added saturated sodium bicarbonate solution and this refluxed for 10 min, the aqueous solution was cooled before it was washed twice with dichloromethane. The

combined washings were dried and the solvent evaporated under reduced pressure to give 150 mg of a mixture of *p*-bromoacetophenone and methyl sulphone.

The aqueous solution was now acidifed with concentrated hydrochloric acid to precipitate the carboxylic acids which were extracted with dichloromethane, the combined organic extracts were dried, and the solvent evaporated under reduced pressure to give 540 mg of material which ^{1}H NMR showed to contain the *title compound* (50f) and *p*-bromobenzoic acid (77) in an approximate ratio of 4.2:1. Methyl sulfone was also present.

The 540 mg mixture was redissolved in dichloromethane and ~5 g of finely powdered sodium bicarbonate was added, the heterogenous mixture stirred at room temperature for 2 d, the salt was filtered off, reacted with concentrated hydrochloric acid, the precipitated carboxylic acid(s) was extracted with dichloromethane, the combined extracts washed with water, dried and the solvent evaporated under reduced pressure to yield *ca.* 130 mg of mainly *p*-bromobenzoic acid (77) which is present as impurity. The dichloromethane filrate was evaporated under reduced pressure to give 410 mg of a mixture of the *title compound* (50f) and methyl sulfone. ^{1}H NMR spectroscopy showed this mixture to be free of *p*-bromobenzoic acid.

Recrystallization of the *title compound (50f):*

The 410 mg mixture collected above was dissolved in almost boiling water (80 ml). As the solution cooled a small amount of brown material settled to the bottom of the flask and an oil settled to the top. This impurity was removed by use of a separating funnel, which ^{1}H NMR spectroscopy showed to be mainly methyl sulfone. To the recrystallizing mixture was added 132 mg of the bromo-acid (50f) that was obtained in an earlier trial reaction and was of similar purity to the material now being recrystallized. All of the epoxide (25f) from the particular borohydride reduction reaction described (p124) was now together again and the final yield is based on this sample of bromo epoxy alcohol (1.2 g, 4.94 mmol). The mixture was redissolved and allowed to cool to 5°C, to obtain 190 mg (0.83 mmol, 17% based on epoxide (25f)) of (*S*)-2-(*p*-bromophenyl)propanoic acid (50f) of mp 104-106°C, $[\alpha]^{20}_D$= 49.0° (10.1 mg/ml EtOH). ^{1}H NMR: δ 1.50 (d, *J* = 7.3 Hz, CH_3), 3.70 (q, *J* = 7.3 Hz, CH), 7.17-7.48 (AA'BB', Ar). ^{13}C NMR: δ 18.00, 44.72, 121.38, 129.34, 131,76, 138.62, 179.65. υ_{max}

(nujol): 3100, 1710 cm^{-1}. Mass spectrum: 229 ($M^{+'}$), 150 (M-Br), 105 (M-Br-CO_2H). $C_9H_9O_2Br$ requires: C, 47.19; H, 3.96; found: C, 47.36; H, 3.69.

(S)-2-[4'-(2''-methylpropyl)phenyl]propanoic Acid (1f):

Coupling performed using modified conditions of Negishi.[59] *iso*-Butyl zinc bromide was prepared by addition of a solution of *iso*-butyl magnesium bromide in ether (0.94 ml, 1.85 M, 1.75 mmol) to a solution of zinc chloride (238 mg, 1.75 mmol, 8 mol equiv.) in THF (8 ml). The mixture was allowed to react for 30 min.

A dry 50 ml Schlenk tube was charged with (*S*)-2-(*p*-bromophenyl)propanoic acid (50f) (50 mg, 0.218 mmol), magnetic stirring bar, tetrakis(triphenylphosphine)palladium(0) (38 mg, 0.033 mmol, 15% equiv.), triphenylphosphine (8.6 mg, 0.033 mmol, 15% equiv.) and dry THF (10 ml). The mixture was taken to 0°C and *iso*-butyl zinc bromide was transferred to the Schlenk tube which was subsequently evacuated and refilled with nitrogen twice before the flask was protected from the light and the mixture stirred under reflux for 4 days, after which time the mixture was black. The reaction was worked up by addition of dilute hydrochloric acid, THF was removed under reduced pressure, and the remaining aqueous solution was extracted with dichloromethane. The combined organic extracts were washed once with water, dried, and the solvent evaporated under reduced pressure to yield 34 mg (0.164 mmol, 75%) of a mixture of ibuprofen (1f), (Rf 0.60 in ethyl acetate/hexane/acetic acid (50:48:2)) and 15% of 2-phenylpropanoic acid (Rf 0.51). Separation by flash chromatography could not be effected with use of this solvent system, however the solvent system ethyl acetate/hexane (1:1)[6] was used to obtain ibuprofen spectroscopically pure. The yield after chromatography was very poor. Ibuprofen was obtained as a colourless oil, which failed to crystallize. ^1H NMR: δ 0.89 (d, J = 6.7 Hz, 6H, Me_2), 1.50 (d, J = 7.0 Hz, 3H, H3), 1.84 (m, J = 6.7 Hz, 1H, H2''), 2.44 (d, J = 7.1 Hz, 2H, H1''), 3.70 (q, J = 7.0, 1H, H2), 7.10 (d, J = 7.8 Hz, 2H, Ar), 7.22 (d, J = 7.8 Hz, 2H, Ar). ^1H NMR data are identical with those of the literature.[61]

Analysis of the optical purity of ibuprofen:

This analysis was kindly performed by P Hayball[44] at Daws Park Hospital. Performed separately with ibuprofen (1f) and an authentic sample of racemic ibuprofen: compounds were derivatized to their respective diastereomeric (*S*)-1-phenylethylamides and chromatographed on a phenyl-bonded phase HPLC column used in reversed-phase mode. Mobile phase was 45% acetonitrile; 1% triethylamine in 20 mM acetate buffer; pH 5.5. A flow rate of 2.0 ml/min was used and uv-absorbance detection at 210 nm. Electronic integration was used to determine the enantiomeric excess which was 96%.

CHAPTER 2

2-(6'-Methoxy-2'-naphthyl)propan-2-ol (79):

A dry flask was charged with magnesium (0.85 g, 0.035 mol, 1.85 mol eq), a few iodine crystals and ether (20 ml). The mixture was left for 2 h before 2-bromo-6-Methoxynaphthyl (4.59 g, 0.019 mol) was added in one portion through a powder funnel and the stirred mixture was refluxed under a nitrogen atmosphere for 18 h. During the first 2 h the suspended bromide dissolved and at the end of the reaction time two layers were present--a brown upper and a yellow lower layer. The mixture was cooled to 0°C and dry acetone was added dropwise, water was then added and the ether was evaporated under reduced pressure. Dichloromethane was added and magnesium salts dissolved by addition of ammonium chloroide solution. The organic layer was washed once with ammonium chloride solution and once with bicarbonate solution before being dried and the solvent removed under reduced pressure and the residue purified by flash chromatography to give the *title compound* in an overall yield of 56% (2.28 g, 0.011 mol) as a white solid. ^{1}H NMR: δ 1.66 (s, 6H), 2.04 (br s, OH), 3.90 (s, 3H, Ar-OCH_3), 7.13-7.86 (m, 6H, Ar). υ_{max} ($CDCl_3$): 3400, 2950, 1620, 1600, 1470, 1255, 1195 cm^{-1}. ^{13}C NMR: δ 31.61, 55.23, 72.50, 105.42, 118.78, 122.22, 123.98, 126.73, 128.50, 129.54, 133.29, 144.17, 157.50.

2-(6'-Methoxy-2'-naphthyl)propene (80):

Prepared according to the method of Yadav.[64] A solution of the alcohol (79) (856 mg, 3.96 mmol), triethylamine (1.65 ml, 11.9 mmol, 3 mol eq), methanesulfonyl chloride (0.76 ml, 9.9 mmol, 2.5 mol eq) and a catalytic amount of dimethylaminopyridine (19 mg, 0.154 mmol, 0.04 eq) in dichloromethane (10 ml) was stirred for 2 h after which time TLC indicated the reaction to be complete. Water (10 ml) was added and the mixture stirred vigorously for 3 h after which time it was extracted twice with dichloromethane. The combined organic extracts were washed once with water, dried and the solvent removed under reduced pressure to give the *title compound* (660 mg, 3.33 mmol, 84%) as a white solid, a sample of which was

recrystallized (hexane) to give crystals of mp 104-106°C (no lit.[64] mp). The alkene decomposes during chromatography on silica or alumina . ^{1}H NMR: δ 2.25 (d, *J* = 1.1 Hz, 3H, H3), 3.91 (s, 3H, Ar-OCH_3), 5.14 (quintet, *J* = 1.1 Hz, 1H, H1), 5.49 (d, *J* = 1.1 Hz, 1H, H1), 7.15-7.79 (m, 6H, Ar). υ_{max} ($CDCl_3$): 3100 (w), 2900, 1620 (s), 1590, 1470, 1250, 1200 cm^{-1}. ^{13}C NMR: δ 21.85, 55.24, 105.56, 112.07, 118.82, 124.06, 124.31, 126.53, 128.72, 129.71, 133.89, 136.11, 142.88, 157.66. Mass spectrum: 198 ($M^{+'}$), 183 (M-CH_3), 155, 139.

(S)-2-(6'-Methoxy-2'-naphthyl)prop-1,2-diol (81f):

This reaction uses material (methoxynaphthyl-) that has not been purified (by chromatography or recrystallization) from the beginning of the reaction series. According to the method of Sharpless,[35] a mixture of water (110 ml), *tert*-butanol (110 ml) and AD-mix-α (26 g) was cooled to 0°C whereupon the alkene (80) (3.35 g, 16.9 mmol) was added and the mixture stirred vigorously at 0°C for 18 h. The reaction was quenched by addition of sodium sulphite (27 g) and the resultant mixture was stirred for 1 h. *tert*-Butanol was removed under reduced pressure and the aqueous residue was extracted twice with dichloromethane. The combined organic phases were washed once with water, dried, filtered through celite and the solvent removed under reduced pressure to give an off-white solid residue which was purified by chromatography with use of a gradient of dichloromethane/ethyl acetate as eluant. The diol is unstable on silica. Recrystallization (ether/hexane, -15°C) gave the diol as a white solid of mp 107-108°C (no lit.[65] mp) in 53% yield (1.73 g, 7.45 mmol, 53% (overall, based on the bromide (78) (16.9 mmol) as this is the first purification and yield calculation in three reactions). ^{1}H NMR: δ 1.56 (s, 3H, H3), 2.2 (br s, 1H, OH), 2.9 (br s, 1H, OH), 3.67 (d, *J* = 11.1 Hz, 1H), 3.84 (d, *J* = 11.1 Hz, 1H), 3.90 (s, 3H, Ar-OCH_3), 7.09-7.84 (m, 6H, Ar). ^{13}C NMR: δ 25.91, 55.25, 70.87, 74.88, 105.38, 118.99, 123.73, 123.82, 126.96, 128.55, 129.55, 133.53, 139.95, 157.67. υ_{max} (nujol): 3200 (br, s), 1620, 1595, 1365, 1195 cm^{-1}. Mass spectrum: 232 ($M^{+'}$), 214, 201, 185. $C_{14}H_{16}O_3$ requires: C, 72.40; H, 6.94; found: C, 72.60; H, 7.13. The optical purity was determined by ^{1}H NMR analysis of the mono-acetate

derivative (85) with the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium(III) derivative and found to be 98% e.e.

(RS)-2-(6'-Methoxy-2'-naphthyl)propan-1,2-diol (81r):

Prepared according to the general method of VanRheenen.[66] A solution of *N*-methylmorpholine *N*-oxide (1.41g, 12.05 mmol, 2.1 eq), aqueous osmium tetroxide solution (quantity unknown), the alkene (80) (1.14 g, 5.74 mmol), in the solvent system of acetone (10 ml) and water (2 ml) was stirred for 40 h. TLC indicated the reaction was not complete however it was worked up by addition of a slurry of sodium hydrosulphite (0.11 g) and florosil (1.1 g) in water (10 ml), the resultant mixture was stirred for 1 h before it was filtered through celite. The acetone was evaporated under reduced pressure and the resultant aqueous mixture was extracted with dichloromethane, the organic layer dried and the solvent removed under reduced pressure. The residue was chromatographed with use of a gradient of dichloromethane/ethyl acetate as eluant to give the diol (81r) (0.81 g, 3.49 mmol, 61%) as a white solid which was recrystallized (ether/hexane) to give powdery crystals of mp 110-111°C. The spectral data are identical with those of the optically active diol.

(RS)-2-(6'-Methoxy-2'-naphthyl)-2-hydroxypropyl Acetate (85r):

A solution of the diol (85r) (37 mg, 0.159 mmol), acetic anhydride (90 µl, 0.96 mmol, 6 eq) and pyridine (1 ml) was stirred for 18 hr before pyridine, acetic acid and excess acetic anhydride were distilled off at 80°C/0.15 T. The product acetate was distilled at 140°C/0.15 T and collected as an oil which slowly solidifed to give a crystals of mp 89-91°C (40 mg, 0.146 mmol, 92%). ^{1}H NMR: δ 1.63 (s, 3H, CH_3), 2.03 (s, 3H, $COCH_3$), 2.7 (br s, OH), 3.91 (s, 3H, Ar-OCH_3), 4.29 (d, J = 11.3 Hz, 1H, OCH_2), 4.39 (d, J = 11.3 Hz, 1H, OCH_2), 7.11-7.87 (m, 6H, Ar). ^{13}C NMR: δ 20.80, 26.57, 55.26, 71.71, 73.67, 105.40, 119.00, 123.63, 123.77, 126.88, 128.53, 129.61, 133.64, 139.36, 157.77, 171.11. υ_{max} ($CDCl_3$): 3500, 3400, 2900, 1720 (s), 1620, 1600 cm^{-1}.

(S)-2-(6'-Methoxy-2'-naphthyl)-2-hydroxypropyl Acetate (85f):

The optically active acetate (85f) was prepared similarly as the racemic acetate (85r). ^{1}H NMR data are identical to those of the racemic material (85r).

(S)-2-(6'-Methoxy-2'-naphthyl)propanol (82f):

This was prepared following ~~According to~~ a general procedure used by Newton.[6] A mixture of the diol (81f) (169 mg, 0.723 mmol), 10% palladium on carbon catalyst (170 mg), perchloric acid (1 mmol, 1.5 ml of a 0.7 mmol/ml solution) in dichloromethane (30 ml) was stirred under an atmosphere of hydrogen for 3 d. The hydrogen atmosphere was evacuated and replaced with air and the mixture filtered through a pad of celite, washing through with dichloromethane. The filtrate was washed once with bicarbonate solution, once with water, dried, the solvent removed under reduced pressure. The residue was chromatographed (30% ethyl acetate/hexane) to give the *title compound* as a white solid (86 mg, 0.40 mmol, 55%). ^{1}H NMR: δ 1.33 (d, J = 7.0 Hz, 3H, CH_3), 1.5 (br s, OH), 3.06 (sextet, J = 7.0 Hz, 1H, CH), 3.74 (d, J = 6.6 Hz, 2H, CH_2), 3.90 (s, 3H, Ar-OCH_3), 7.10-7.71 (m, 6H, Ar). ^{13}C NMR: δ 17.61, 42.32, 55.28, 68.59, 105.53, 118.88, 125.87, 126.23, 127.18, 128.98, 129.06, 133.49, 138.60, 157.38. υ_{max} ($CDCl_3$): 3550, 2850, 1620, 1600, 1470, 1250 cm^{-1}. Mass spectrum: 216 ($M^{+\cdot}$), 205, 185 (M-CH_2OH), 172.

(R)-2-[2'-(6''-Methoxynaphthyl)]-2-chloropropyl Acetate (92f):

This was Prepared according to the method of Sharpless.[72] A solution of the diol (81f) (61 mg, 0.26 mmol), trimethylorthoacetate (200 µl, 1.29 mmol, 3 eq), trimethylchlorosilane (200 µl, 1.29 mmol, 3 eq) in dichloromethane (1 ml) was stirred for 3 h before the reaction was worked up by evaporation of by-products, excess reagents and solvent under reduced pressure to give the *title compound* in quantitative yield. ^{1}H NMR: δ 2.04 (s, 3H, CH_3), 2.08 (s, 3H, $COCH_3$), 3.92 (s, 3H, Ar-OCH_3), 4.52 (d, J = 11.6 Hz, 1H, CH_2O), 4.59 (d, J = 11.6 Hz, 1H, CH_2O), 7.12-7.87 (m, 6H, Ar). υ_{max} ($CDCl_3$): 2950, 1730 (s), 1620 (w), 1600, 1470, 1230 cm^{-1}. Mass spectrum: 294, 292 ($M^{+\cdot}$), 257 (M-Cl), 219, 221 (M-CH_2OAc), 184 (221-Cl).

Attempt to form *(S)-2-(6'-Methoxy-2'-naphthyl)-2-methlyoxiraine (91f):*

Formation of *(S)-2-(6'-Methoxy-2'-naphthyl)-2-methoxypropanol (93f):*

Prepared according to the procedure of Sharpless.[72] To a solution of the chloroacetate (92f) (76 mg, 0.26 mmol) in methanol (1.5 ml) was added potassium carbonate (36 mg, 0.26 mmol) and the mixture stirred 2 h. Dichloromethane (20 ml) was added and dilute ammonium chloride solution. The aqueous phase was extracted twice with dichloromethane, the combined organic phases washed once with water, dried and the solvent removed under reduced pressure and the residue purified by chromatography on silica (5% triethylamine/dichloromethane/ hexane) to give the *title compound* in 40% yield (25 mg, 0.10 mmol). ^{1}H NMR: δ 1.72 (s, 3H, H3), 2.2 (poorly defined t, J = 7.1 Hz, 1H, OH), 3.17 (s, 3H, C2-OCH_3), 3.58 (dd, J = 10.8, 7.1 Hz, 1H, CH<u>H</u>), 3.77 (d, J = 10.8 Hz, 1H, C<u>H</u>H), 3.92 (s, 3H, Ar-OCH_3), 7.14-7.76 (m, 6H, Ar). Mass spectrum: 246 ($M^{+\cdot}$).

(S)-2'-(6''-Methoxy-2''-naphthyl)-2'-hydroxypropyl-4-toluenesulphonate (94f):

Prepared according to the general method of Sharpless.[73] To a solution of the diol (81f) (228 mg, 0.98 mmol) and pyridine (400 µl, 4.91 mmol, 5 eq) in dichloromethane (5 ml) was added tosyl chloride (375 mg, 1.96 mmol, 2 eq). The reaction mixture was stirred for 3 d at room temperature before it was worked up by partial evaporation of dichloromethane, the residue loaded directly onto a column of silica and eluted with 5% triethylamine/65% hexane/ dichloromethane. Pyridine is eluted first, then the epoxide (91f), and then the tosylate (94f) as a yellow band. No yield was recorded as both epoxide (91f) and tosylate (94f) were present and chromatography did not give complete separation. ^{1}H NMR: δ 1.62 (s, 3H, H3), 2.37 (s, 3H, tosyl-CH_3), 3.90 (s, 3H, Ar-OCH_3), 4.16 (s, 2H, CH_2), 7.08-7.76 (m, 6H, Ar). Mass spectrum: 386 ($M^{+\cdot}$), 369 (M-OH), 307, 289, 279, 215 (M-TsO), 201 (M-$TsOCH_2$).

(S)-2-(6'-Methoxy-2'-naphthyl)-2-methlyoxiraine (91f):

Prepared according to the general method of Sharpless.[73] Absolutely dry conditions are essential in the reaction. To a stirred suspension of sodium hydride (excess, unweighed, washed free of oil with dry benzene under an atmosphere of nitrogen) in dry THF (2.5 ml)

was added the tosylate (94f) (88 mg, 0.30 mmol, mixture which also contains epoxide (91f)). After the reaction mixture was stirred for 2.5 h, dichloromethane (20 ml) was added and the reaction worked up by cautious addition to ammonium chloride solution. The aqueous solution was extracted twice with dichloromethane, the combined organic extracts washed once with water, dried, and the solvent removed under reduced pressure to give the epoxide (91f) quantitatively (53 mg, 0.23 mmol) as a white solid. Further purification was not necessary. A small sample was recrystallized from hexane to give fluffy white crystals of mp 86-88°C. ^{1}H NMR: δ 1.79 (s, 3H, CH_3), 2.88 (d, J = 5.3 Hz, 1 H, CHH), 3.02 (d, J = 5.3 Hz, 1H, CHH), 3.90 (s, 3H, Ar-OCH_3), 7.10-7.77 (m, 6H, Ar). ^{13}C NMR: δ 21.88, 55.26, 56.90, 57.09, 105.51, 199.05, 123.66, 124.27, 126.91, 128.54, 129.38, 133.82, 136.25, 157.72. υ_{max}: 2900, 1620 (w), 1600, 1470, 1190 cm^{-1}.

(S)-2-(6'-Methoxy-2'-naphthyl)propanol (82f):

The method used was that of Sugi.[42] To a solution of the epoxide (91f) (30.6 mg, 0.143 mmol) in ethanol (15 ml) was added 10% palladium on carbon catalyst (50 mg) and four drops of a 10% solution of sodium hydroxide. The air was replaced with a hydrogen atmosphere by successively evacuating and refilling. The mixture was stirred at room temperature for 18 h before the hydrogen atmosphere was replaced with air and the palladium catalyst filtered off through celite. Water (10 ml) was added and the ethanol was removed under reduced pressure, before the aqueous phase was extracted with dichloromethane. The combined organic phases were dried and the solvent removed under reduced pressure to give the *title compound* as a white solid (28.4 mg, 0.131 mmol, 92%). A portion was recrystallized from ether/hexane to give powdery crystals of mp 82-4°C (lit.[75] mp 88-9°C). Spectral data for the alcohol (82f) have been presented (p132). Optical purity was determined by conversion to the Mosher ester, which is detailed below, and integration of the methoxy methyl signals of the two diastereomers. This gave an optical purity of 89%. Oxidation of this sample to naproxen, which was determined to have an optical purity of 91% (which is in experimental error), confirmed this.[75]

The hydrogenolysis was repeated with the following conditions: the epoxide (91f) (14.6 mg, 0.682 mmol), palladium on carbon (26 mg), 3 drops of 10% sodium hydroxide solution in ethanol (20 ml). The reaction mixture was stirred for 18 hr at -40°C before it was worked up as described above to obtain the *title compound* in 92% yield (13.5 mg, 0.0625 mmol). The optical purity was determined to be 97% via the Mosher ester.

Determination of optical purity of the alcohol (82f):

(2R,2''S)- and *(2R,2''R)-2'-(6''-Methoxy-2''-naphthyl)propyl 2-Methoxy-2-trifluoro-methylphenylacetate (95)* and *(96)* respectively:

Prepared according to the general procedure of Hassner.[74] A mixture of the racemic alcohol (82r) (4.0 mg, 0.018 mmol), dicyclohexylcarbodiimide (15 mg, 0.083 mmol, 4 eq), dimethylaminopyridine (1 mg, cat.) and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (15 mg, 0.064 mmol, 4 eq.), in dichloromethane (1 ml) was stirred 18 h. The reaction mixture was diluted with dichloromethane and worked up by addition of water, the mixture was filtered through a cotton wool plug, the phases separated, and the organic phase washed successively with 10% sodium hydroxide solution, 10% hydrochloric acid solution and with water before being dried and the solvent removed under reduced pressure. The residue was chromatographed, (dichloromethane) to give the *title diastereomeric mixture* in 69% yield (5.5 mg, 0.013 mmol). ^{1}H NMR (of (96)): δ 1.37 (d, J = 7.1 Hz, 3H, H3), 3.31 (sextet, J = 7.1 Hz, 1H, H2), 3.41 (q, J = 1.0 Hz, 3H, C-OCH_3), 3.92 (s, 3H, Ar-OCH_3), 4.37 (dd, J = 10.8, 6.6 Hz, 1H, H1), 4.60 (dd, J = 10.8, 6.6 Hz, 1H, H1), 7.11-7.68 (m, 11H, Ar, Ph).

(2R,2''S)-2'-(6''-Methoxy-2''-naphthyl)propyl 2-Methoxy-2-trifluoromethylphenyl-acetate (95):

Prepared as for the diastereomeric mixture with use of a different work-up. A mixture of the optically active alcohol (82f) (5.2 mg, 0.024 mmol), dicyclohexylcarbodiimide (17 mg, 0.11 mmol, 4 eq), dimethylaminopyridine (1 mg, cat.) and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (25 mg, 0.072 mmol, 4 eq.), in dichloromethane (2 ml) was

stirred for 18 h. The mixture was loaded directly onto a column of silica and eluted with dichloromethane (the diastereomers co-run on silica). The Mosher ester(s) eluted first, as a solid (8.0 mg, 0.019 mmol, 77%). ^{1}H NMR (of (95)): δ 1.37 (d, *J* = 7.1 Hz, 3H, H3), 3.30 (sextet, *J* = 7.1 Hz, 1H, H2), 3.37 (q, *J* = 1.0 Hz, 3H, C-OCH$_3$), 3.92 (s, 3H, Ar-OCH$_3$), 4.40 (dd, *J* = 10.8, 6.6 Hz, 1H, H1), 4.55 (dd, *J* = 10.8, 7.6 Hz, 1H, H1), 7.11-7.68 (m, 11H, Ar, Ph).

(RS)-2-(6'-Methoxy-2'-naphthyl)propanoic Acid (2r):

To a solution of the alcohol (82r) (16 mg, 0.074 mmol) in acetone (2 ml) and water (0.5 ml) at 0°C was added 7 drops of Jones' reagent and the mixture stirred for 20 min. The reaction was quenched by addition of sodium thiosulphate solution (1.5 ml), sodium bicarbonate solution (1.5 ml) and heating at 60°C for 5 min. Acetone was removed under reduced pressure, water was added and the mixture washed once with dichloromethane, the aqueous was acidified with 10% hydrochloric acid and extracted twice with dichloromethane. The combined organic extractions were dried and the solvent removed under reduced pressure to give racemic naproxen in quantitative yield (17 mg, 0.073 mmol). The organic washing was dried, and the solvent removed under reduced pressure to give a neutral by-product (1.6 mg). ^{1}H NMR: δ 1.59 (d, *J* = 7.2 Hz, 3H, H3), 3.87 (q, *J* = 7.2 Hz, 1H, H2), 3.91 (s, 3H, OC<u>H</u>$_3$), 7.10-7.71 (complex, 6H, Ar) (spectral data match that reported[71]).

(S)-2-(6'-Methoxy-2'-naphthyl)propanoic Acid (2r):

Oxidation of the alcohol (82f), prepared at -40°C, to (*S*)-naproxen was carried out as above with the alcohol (82r) (9.2 mg, 42.6 μmol) and 9 drops of Jones reagent. Work-up which involved an accidental spillage yielded (*S*)-naproxen in 38% yield (3.7 mg, 16.1 μmol). Recrystallization from hexane gave a mp of 151-3°C (lit.[75] 152-4°C). The optical purity was determined by reaction of naproxen with a molar equivalent of optically pure cinchonidine, and integration of the methyl signals of naproxen in the ^{1}H NMR spectrum. The cut-and-weigh method of integration gave an e.e. of 96%. ^{1}H NMR data of (2f) are identical of those of (2r).

CHAPTER 3

2-Benzoylpyrrole (104):

Preparation of *Benzoylmorphilide (111):*

Prepared according to the method of McGillivray.[80] Reagents and substrates for this reaction were dried and distilled. To a solution of benzoyl chloride (22.3 ml, 0.193 mol) and triethylamine (20 g, 0.20 mol, 28 ml) in toluene (200 ml), in a dry flask which was being agitated vigorously by hand, was added morpholine (17 ml, 0.195 mol), over a period of 15 min. The mixture became increasingly thick during this time, as triethylamine hydrochloride formed. The flask was cooled periodically in ice/water during the addition and was subsequently let stand at room temperature for 2 h before the reaction was worked up by washing the mixture with water. The washings were extracted twice with dichloromethane and the combined extractions and toluene phase were washed once with water, dried, and the solvent removed under reduced pressure to give the amide (111) as an oil which crystallized on addition of a seed crystal of the amide (111). This was recrystallized from hexane/toluene (250 ml/70 ml) to give long white needles in a yield of 84% (30.8 g, 0.161 mol) with a melting point of 73-74°C. ^{1}H NMR: d 3.4-3.9 (poorly resolved multiplet, 8H, NCH_2CH_2O), 7.36-7.41 (mutiplet, Ar-H).

A mixture of doubly redistilled phosphoryl chloride (32.2 g, 0.346 mol, 2.15 equiv) and the amide (111) from above (30.75 g, 0.161 mol) was stirred for 18 hr in a dry 1 l flask. A precipitate had formed to which was added a solution of pyrrole (10.4 ml, 0.161 mol) in dichloroethane (800 ml) and the mixture resulant mixture allowed to stir for 24 h after which time UV spectroscopy indicated that the reaction had gone to completion by an increase in the absorption in the 350-400 nm region, of an aliquot taken from the reaction mixture. Work-up was achieved by cautious addition of a 10% solution of sodium carbonate to the vigorously stirred reaction mixture. This bi-phasic mixture was refluxed for 30 min, cooled, the layers separated, and the aqueous phase extracted with dichloromethane. The combined organic

phases were washed once with water, dried over sodium carbonate, and the solvent evaporated under reduced pressure to give a pale pink solid which was recrystallized from hexane to give large pale-pink crystals with a melting range of 72-79°C in 66% yield (18.1 g), a red oil had also precipitated out, and this and the mother liquor was put through a short squat column to give another 25% yield (7.1 g) as a pale pink solid. ^{1}H NMR (200 MHz): d 6.33 (dd, *J* = 2.5, 3.8 Hz, 1H), 6.89 (dd, *J* = 1.3, 3.8 Hz, 1H), 7.18 (dd, *J* = 2.5, 1.3 Hz, 1H), 7.41-8.01 (m, 5H, Ar), 10.6 (br s, 1H, NH). u_{max}: 3260, 1620 cm^{-1}. Mass spectrum: 171 ($M^{+\prime}$), 105 ($M^{+\prime}$-py), 94, 77.

3-(2'-Benzoylpyrrolyl)propanenitrile (105):

According to a general procedure of Patterson,[82] to a stirred solution of 2-benzoylpyrrole (23.98 g, 0.14 mol) and Triton B (1 ml) in dioxane (35 ml) was added acrylonitrile (11 ml, 0.21 mol, 1.5 equiv) over a period of 10 mins, with cooling in an ice bath. The reaction mixture was stirred in the dark for 42 h after which time the mixture was coloured dark red and a large amount of precipitate had formed. The flask was placed under reduced pressure to remove methanol and excess acrylonitrile before dichloromethane (200 ml) was added and the resultant solution washed twice with water, dried, and the solvent removed under reduced pressure, the last traces of dioxane were removed under high vacuum. This gave the crude *title compound* in a yield of 105% (32.87 g) which was chromatographed (30% ethyl acetate/hexane) through a 1 cm high column of silica to remove polymeric material.

Recrystallization the *title compound* from hexane (300 ml) and dichloromethane (100 ml) was unsuccessful as decomposition occurred on heating. The impure crystals had a melting range of 82-87°C. ^{1}H NMR: δ 3.02 (t, *J* = 6.3 Hz, CH_2CN), 4.61 (t, *J* = 6.3 Hz, N-CH_2), 6.24 (dd, *J* =4.2, 2.6 Hz, 1H), 6.83 (dd, *J* = 4.2, 1.7 Hz, 1H), 7.11 (dd, *J* = 2.6, 1.7 Hz, 1H), 7.41-7.58 (m, 3H, Ar-H), 7.76-7.80 (m, 2H, Ar-H). ^{13}C NMR: δ 20.20, 45.19, 109.08, 117.55, 124.11, 128.00, 128.91, 129.29, 131.29, 131.50, 139.27, 186.01. υ_{max}: 2250, 1620, 1610, 1600, 1580, 1530 cm^{-1}. Mass spectrum: 224 ($M^{+\prime}$), 184 ($M^{+\prime}$ - CH_2CN), 147, 105, 77.

*1-Keto-1,2-dihyro-3*H*-pyrrolo[1,2-*a*]pyrrole (113):*

To a solution of *N*-(2-cyanoethyl)pyrrole (1.0 g, 8.3 mmol) in ether (40 ml) was added boron trifluoride etherate (4.2 ml, 34 mmol, 4.1 equiv.) under dry conditions.

Dry hydrogen chloride gas was generated by dropwise addition of concentrated sulphuric acid to a stirred and cooled solution of 30% hydrochloric acid, and dried by bubbling through concentrated sulphuric acid.

This hydrogen chloride gas was bubbled through the ice cooled reaction mixture until saturated, at which point the gas was no longer absorbed and was visibly seen at the escape vent. During this time orange precipitate formed and coated the sides of the flask. The flask was stoppered and the reaction mixture allowed to stir in the dark for 48 h before the stopper was removed and nitrogen gas blown over the heated reaction mixture to allow hydrogen chloride gas to evaporate. The residue was azeotroped with ether three times under reduced pressure to remove boron trifluoride etherate. Water (50 ml) and sodium acetate (4.3 g) was added and the mixture heated at 70°C for 18 h during which time the red residue dissolved. The aqueous solution was cooled, extracted with dichloromethane, the combined organic phases were washed once with water, dried, and the solvent evaporated under reduced pressure to give the *title compound* in quantitative yield (1.0 g). The ^{1}H NMR spectrum of the crude material showed the compound to be very clean. ^{1}H NMR: δ 3.08 (t, *J* =6.1 Hz, 2H, H2), 4.31 (t, *J* = 6.1 Hz, 2H, H3), 6.52 (dd, *J* = 3.9, 2.0 Hz, 1H), 6.73 (dd, *J* = 3.9, 0.8 Hz, 1H), 7.04 (dd, *J* = 2.0, 0.8 Hz, 1H). υ_{max} ($CDCl_3$): 1700, 1530 cm^{-1}. Mass spectrum: 121 ($M^{+\cdot}$), 93 ($M^{+\cdot}$-CO).

Attempt to cyclize *3-(2'-Benzoylpyrrolyl)propanenitrile (105):*

Formation of *3-(2'-Benzoylpyrrolyl)propanamide (114):*

To a solution of the nitrile (105) (500 mg, 2.23 mmol) in dry ether (20 ml) was added boron trifluoride etherate (1.1 ml, 8.93 mmol, 4 equiv). Dry hydrogen chloride gas was bubbled through the ice cooled reaction mixture until the mixture was saturated. During this time the yellow reaction mixture became orange. The flask was sealed and the reaction mixture allowed to stir in the dark for 65 h after which time the mixture was dark red and a red

precipitate had formed. The stopper was removed and nitrogen gas was blown through the heated mixture to remove hydrogen chloride gas. The residue was azeotroped with ether three times under reduced pressure to remove boron trifluoride etherate. Water (50 ml) and sodium acetate (5 g) were added and the mixture heated at 70°C for 3 h during which time the red residue dissolved. The aqueous solution was cooled, extracted with dichloromethane, the combined organic phases were washed once with water, dried, and the solvent evaporated under reduced pressure to give the *title compound* . No yield was measured, however on a repetition of this reaction a crude yield of 74% was obtained, which ^{1}H NMR spectroscopy indicated was of high purity. The melting range was 148-160°C with decomposition from 110°C. Further purification by recrystallization was unsuccessful as the compound was too unstable. ^{1}H NMR: δ 2.83 (t, *J* = 6.8 Hz, 2H), 4.65 (t, *J* = 6.8 Hz, 2H), 5.5 variable (br s, 1H, NH_2), 6.0 variable (br s, 1H, NH_2), 6.18 (dd, *J* = 4.1, 2.5 Hz, 1H), 6.78 (dd, *J* = 4.0, 1.5 Hz, 1H), 7.10 (dd, *J* =4.1, 1.8 Hz, 1H), 7.43-7.55 (m, 3H, Ar-H), 7.76-7.80 (m, 2H, Ar-H). υ_{max}: 3350, 3150, 1700, 1690, 1620, 1610, 1600, 1560, 1520 cm^{-1}.

Attempts at preparation of *3-(2'-Benzoylpyrrolyl)propanamide (114):*

Attempt #1:

A flask which contains a solution of the nitrile (105) (160 mg) in THF (3 ml) and concentrated hydrochloric acid (3 ml) was stoppered. The mixture was stirred and heated at 40°C for 2.5 h after which the THF was removed under reduced pressure and the aqueous solution was extracted with dichloromethane. The organic extract was dried and the solvent removed under reduced pressure to reveal, by ^{1}H NMR spectroscopy, that no change had occured.

Attempt #2:

A stirred solution of the nitrile (105) (210 mg) in THF (1.5 ml) and a 1:5 triflic acid/water mixture (1.5 ml) was refluxed for 18 hr. Aqueous sodium bicarbonate solution was added, THF removed under reduced pressure and the aqueous residue extracted with dichloromethane. The organic phase was dried and evaporated under reduced pressure. ^{1}H NMR spectroscopy revealed that no change had taken place.

Attempted preparation of N,N-*dimethyl-3-(2'-Benzoylpyrrolyl)propanamide (115):*

Attempt #1:

According to a general methylation procedure by Johnstone,[85] to a partially dissolved heterogeneous mixture of powdered potassium hydroxide (2.9 g, 43 mmol, 8 equiv.) in DMSO (11 ml) was added the unsubstituted amide (114), (1.30 g, 5.37 mmol) and methyl iodide (3.05 g, 21.5 mmol, 4 equiv). The reaction mixture was stirred for 15 min whereupon ammonium chloride (3 g) was added and the mixture stirred another 5 min. DMSO was removed by distillation under high vacuum at 60°C. To the residue was added dichloromethane and the resulting solution was washed three times with water, dried, and the solvent removed under reduced pressure to give 0.915 g of a mixture that was flash chromatographed (15% ethyl acetate/dichloromethane) to give two compounds that were determined to be 2-benzoylpyrrole[80] and 1-methyl-2-benzoylpyrrole[86] by ^{1}H NMR spectroscopy.

Attempt # 2:

Preparation of N,N-*dimethylacrylamide (118):*

To a dry 100 ml flask was added dry carbon tetrachloride, a magnetic stirring bar and acryl chloride (5 g, 55 mmol, 4.5 ml), before the flask was sealed with a septum. The flask was immersed in ice water and dimethylamine (bp 7°C) was added portionwise through a needle in the septum to the stirred reaction mixture. The reaction was seen to be complete by the absence of dimethyl ammonium chloride smoke on further addition of the amine. Dichloromethane was added, the resulting solution washed once with 20% sodium carbonate solution, twice with water, dried, and the solvent was evaporated under reduced pressure to give the *title compound* in 82% yield (4.48 g, 45 mmol), which was used without further purification. ^{1}H NMR: δ 3.02 (s, CH_3), 3.10 (s, CH_3), 5.67 (dd, J = 2.3, 10.7 Hz, 1H), 6.29 (dd, J = 2.3, 16.9 Hz, 1H), 6.60 (dd, J = 10.7, 16.9 Hz, 1H).

To a stirred solution of 2-benzoylpyrrole (7.62 g, 45 mmol) in dioxane (25 ml) was added *N,N*-dimethylacrylamide (4.5 g, 45 mmol) and Triton B (0.3 ml). After the reaction mixture was stirred for 2 d, TLC analysis showed that starting material was still present. The reaction

mixture was thus heated at 60°C for 15 h after which time TLC analysis indicated that no apparent change had occurred. The reaction mixture was refluxed for 15 h, however again no change was apparent.. Dichloromethane was added and the resultant solution washed twice with water to remove Triton B. The solvent was removed under reducted pressure and the resultant mixture of 2-benzoylpyrrole and acrylamide (118) used in the next step.

To a suspension of sodium hydride (80% dispersion in mineral oil, 78 mg, 2.2 mmol, 1.5 equiv) in dry DMF (3 ml) in a 50 ml flask was added dropwise the mixture from above (1.25 ml) containing 2-benzoylpyrrole (1.5 mmol) and *N,N*-dimethylacrylamide (1.5 mmol). The mixture was stirred at room temperature for 3 h before being worked up by addition of ammonium chloride (117 mg, 2.2 mmol). The solvent was removed under reduced pressure, dichloromethane was added to the residue and the resultant solution washed twice with water, dried, and the solvent removed under reduced pressure to return 2-benzoylpyrrole as seen by ^{1}H NMR spectroscopy.

Attempted preparation of *3-(2'-Benzoylpyrrolyl)propanenitrile Ethylene Acetal (119):*

A solution of 3-(2'-Benzoylpyrrole)propanenitrile (1.0 g, 4.5 mmol), ethylene glycol (0.83 g, 13.4 mmol, 3 equiv) and *p*-toluenesulphonic acid (0.17 g, 0.892 mmol, 0.2 equiv) in benzene (60 ml) was refluxed through a Dean-Stark trap for 15 h before the azeotroped liquid in the trap was identified as the glycol by observation of the diffraction differential, and density (ethylene glycol d= 1.113 g/ml) of the collected liquid in water. Benzene was removed from the reaction mixture under reduced pressure and the residue identified by ^{1}H NMR spectroscopy as starting material and another unidentified compound.

Attempted benzoylation of *1-Keto-1,2-dihyro-3*H*-pyrrolo[1,2-a]pyrrole (113):*

Following a benzoylation procedure of Muchowski[83] a dry 250 ml flask was charged with *N,N*-dimethylbenzamide (1.07 g, 7.15 mmol, 1 mol equiv), 2-ethoxyethyl ether (80 ml), a magnetic stirring bar and oxalyl chloride (0.86 g, 6.8 mmol, 0.95 equiv, 0.60 ml) and was capped with a drying tube. The mixture was stirred at room temperature for 2 h, heated at 50°C for 30 min before it was placed under vacuum for 10 min while still at 50°C. Some

precipitate was present at this time. The ketone (113) (0.52 g, 4.26 mmol, 0.6 equiv) was subsequently added and the mixture heated at 140°C for 40 h, during which time the colour darkened and precipitate formed. The reaction was quenched by addition of sodium acetate (3 g) and water (20 ml) and refluxing the resultant mixture for 4 h with vigorous stirring before the polyether solvent was removed under high vacuum. Dichloromethane was added to the residue and the resulting solution washed twice with water, dried, and the solvent removed under reduced pressure to give a brown oil which was eluted through a short squat column to remove baseline material. ^{1}H NMR spectroscopy of the crude reaction mixture indicated starting pyrrole (113) as the only pyrrolic substance present, the starting amide (111) and some remaining polyether.

Ethyl 3-(2'-Benzoylpyrrolyl)propanoate (120):

Following the procedure for the preparation of 3-(2'-benzoylpyrrolyl)propanenitrile (p139) the following quantities were used: 4.03 g (23.7 mmol) of 2-benzoylpyrrole, 2.8 ml (25.8 mmol, 1.1 equiv) of ethyl acrylate, 0.02 ml of Triton B and 20 ml of dioxane. Work-up yielded of the crude *title compound* in 99% yield (6.48 g) as a low melting, off-white solid that was not further purified. ^{1}H NMR: δ 2.92 (t, J = 6.5 Hz, 2H), 4.67 (t, J = 6.5 Hz, 2H), 6.15 (dd, J = 4.0, 2.5 Hz, 1H), 6.76 (dd, J = 3.9, 1.4 Hz, 1H), 7.07 (dd, J = 4.0, 2.1 Hz, 1H), 7.41-7.53 (m, 3H, Ar-H), 7.76-7.79 (m, 2H, Ar-H). υ_{max}: 1730, 1610, 1600, 1575 cm^{-1}.

3-(2'-Benzoylpyrrolyl)propanoic Acid (124):

To a stirred aqueous solution (20 ml) of sodium hydroxide (2.74 g, 68.6 mmol, 3 equiv) was added the ester (123) (6.24 g, 23.0 mmol) from above. The reaction mixture was heated at 100°C for 50 min before it was worked up by addition of 15% hydrochloric acid. The aqueous mixture was extracted twice with dichloromethane, the combined organic phases were washed once with water, dried, and the solvent evaporated under reduced pressure to the *title compound* as a red coloured solid, in a of yield 90% (5.04 g, 20.7 mmol). A portion of this was recrystallized from water to give white flakey crystals of melting point 114-116°C. ^{1}H NMR: δ 3.00 (t, J = 6.5 Hz, 2H, $NCH_2C\underline{H}_2$), 4.66 (t, J = 6.5 Hz, 2H, $NC\underline{H}_2CH_2$), 6.16

(dd, J = 2.7, 4.2 Hz, 1H), 6.77 (dd, J = 1.8, 4.1 Hz, 1H), 7.08 (dd, J = 1.8, 2.7 Hz, 1H), 7.24-7.56 (m, 3H, Ar-H), 7.76-7.79 (m, 2H, Ar-H). ^{13}C NMR: δ 35.9, 44.8, 108.5, 124.1, 128.0, 129.1, 129.4, 131.4, 131.8, 139.6, 177.2, 186.1. υ_{max}: 3210, 1730, 1620, 1570, 1530 cm^{-1}. Mass spectrum: 243 ($M^{+\cdot}$), 166 (M - Ph), 105 ($PhCO^+$).

Attempted cyclization of *3-(2'-Benzoylpyrrolyl)propanoic Acid (124):*

Attempt #1: formation of *6-benzoyl-1-keto-1,2-dihyro-3*H*-pyrrolo[1,2-a]pyrrole (125)* and *3-(3'-benzoylpyrrolyl)propanoic acid (126):*

A mixture of the acid (124) (88 mg, 0.36 mmol) and polyphosphoric acid (20 g) was heated while it was stirred vigorously at 100°C for 30 min under a dry atmosphere. The reaction was worked up by cautious addition of water and solid sodium carbonate, the resultant mixture was stirred and warmed. It was then cooled and extracted twice with dichloromethane, the combined extractions were washed once with water, dried, and the solvent removed under reduced pressure to give 6-benzoyl-1-keto-1,2-dihyro-3*H*-pyrrolo[1,2-*a*]pyrrole (125) (8 mg, 0.04 mmol, 10% yield). ^{1}H NMR: δ 3.14 (t, J = 6.5 Hz, 2H, CH_2CO), 4.41 (t, J = 6.5 Hz, 2H, N-CH_2), 7.11 (d, J =1.0 Hz, 1H), 7.64 (d, J = 1.0 Hz, 1H), 7.45-7.57 (m, 3H, Ar-H), 7.81-7.78 (m, 2H, Ar-H). ^{13}C NMR: 39.0, 42.5, 109.0, 126.8, 128.2, 128.8, 130.9, 132.0, 132.1, 132.5, 138.5, 190.0, 190.5. υ_{max}: 3150, 1705, 1635, 1630, 1600, 1580, 1540 cm^{-1}. Mass spectrum: 225 ($M^{+\cdot}$), 148 (M - Ph), 120 (M - Ph - CO). The aqueous phase from above was acidified with concentrated hydrochloric acid before it was extracted twice with dichloromethane, the combined extractions washed once with water, dried, and the solvent evaporated under reduced pressure to give 3-(3'-benzoylpyrrolyl)propanoic acid (126) (70 mg, 0.29 mmol, 80%). ^{1}H NMR: δ 2.87 (t, J = 6.5 Hz, N-$CH_2C\underline{H}_2$), 4.25 (t, J = 6.5 Hz, N-$C\underline{H}_2CH_2$), 6.68 (dd, J = 2.6, 1.8 Hz, 1H), 6.71 (dd, J = 2.6, 1.8 Hz, 1H), 7.29 (dd, J = 1.8, 1.8 Hz, 1H), 7.42-7.53 (m, 3H, Ar-H), 7.79-7.82 (m, 2H, Ar-H). υ_{max}: 1720, 1585, 1565, 1525 cm^{-1}.

Attempt #2: formation of *7-benzoyl-1-keto-1,2-dihyro-3*H*-pyrrolo[1,2-a]pyrrole (127):*

Using the above procedure the acid (124) (307 mg, 1.26 mmol) was allowed to react in polyphosphoric acid (46 g) at 100°C for 4.75 h to give a 65% yield of crude neutral material of

(185 mg, 0.82 mmol) which was chromatographed (50% ethyl acetate/dichloromethane) to give the 6-benzoyl (126) and 7-benzoyl (127) isomers of the desired cyclized product. ^{1}H NMR of (127): δ 3.15 (t, *J* = 6.3 Hz, N-$CH_2C\underline{H}_2$), 4.40 (t, *J* = 6.3 Hz, N-$C\underline{H}_2CH_2$), 6.92 (d, *J* = 2.6 Hz, 1H), 7.06 (d, *J* = 2.6 Hz, 1H), 7.43-7.60 (m, 3H, Ar-H), 7.79-7.90 (m, 2H, Ar-H).

3-(2'-Benzoylpyrrolyl)propanoyl Chloride (128):

To a stirred solution of the acid (124) (300 mg, 1.23 mmol) in benzene (10 ml) under dry conditions was added oxalyl chloride (0.6 ml, 6.17 mmol, 5 equiv). The reaction mixture was stirred at room temperature for 3 h before the product was isolated by removal of the solvent and excess reagent under reduced pressure, first at 100 mmHg/25°C and subsequently at 0.02 T. ^{1}H NMR: δ 3.58 (t, *J* = 6.1 Hz, N-$CH_2C\underline{H}_2$), 4.66 (t, *J* = 6.1 Hz, N-$C\underline{H}_2CH_2$), 6.19 (dd, *J* = 4.0, 2.6 Hz, 1H), 6.80 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.07 (dd, *J* = 1.6, 2.6 Hz, 1H), 7.41-7.55 (m, 3H, Ar-H), 7.70-7.79 (m, 2H, Ar-H). υ_{max} ($CDCl_3$): 1790, 1630, 1600, 1580, 1530 cm^{-1}.

Attempted cyclization of *3-(2'-Benzoylpyrrolyl)propanoyl Chloride (128):*

Attempt #1:

To a stirred solution of the freshly prepared acid chloride (128) (134 mg, 0.513 mmol) in chloroform (10 ml) under dry conditions was added aluminium trichloride (250 mg, 1.80 mmol, 3.5 equiv). The mixture was refluxed for 1.25 h to form a red coloured solution which was worked up by acidification to pH 2 with 15% hydrochloric acid. The resultant mixture was extracted twice with dichloromethane, the combined extractions were washed once with water, dried, and the solvent removed under reduced pressure to yield 113 mg of crude material which ^{1}H NMR spectroscopy indicated was the carboxylic acid (124); resonances due to the desired cyclized material (106) were present at *ca.* 5% relative intensity.

Attempt #2:

Nitrobenzene was by stirred vigorously over anhydrouys calcium chloride before it was decanted from the salt and distilled from phosphorous pentoxide under reduced pressure.

A stirred solution of freshly prepared acid chloride (128) (50 mg, 0.19 mmol) in dry nitrobenzene (20 ml) was heated under dry conditions for 18 h at 170°C. The reaction mixture was worked up by removal of nitrobenzene under high vacuum and anhydrous conditions. The ^{1}H NMR spectrum of the crude material showed the presence of resonances due to the desired cyclized material (106) (*ca.* 20%), the anhyride (132) (*ca.* 20%), and the carboxylic acid (124) (*ca.* 60%).

Attempt #3: formation of *3-(2'-Benzoylpyrrolyl)propanoic Anhydride (132):*

A stirred solution of the freshly prepared acid chloride (128) (100 mg, 0.38 mmol) in dry nitrobenzene (2 ml) was heated under dry conditions for 18 h at 145°C. The reaction mixture was worked up by removal of the solvent under high vacuum and anhydrous conditions to give the anhydride (132) as the only pyrrolic product. Water (0.19 mmol, 0.5 equiv) entered the reaction mixture in some way. ^{1}H NMR: δ 3.09 (t, J = 6.3 Hz, N-$CH_2C\underline{H}_2$), 4.65 (t, J = 6.3 Hz, N-$C\underline{H}_2CH_2$), 6.15 (dd, J = 2.6, 4.1 Hz, 1H), 6.77 (dd, J = 1.5, 4.1 Hz, 1H), 7.09 (dd, J = 2.6, 1.5 Hz, 1H), 7.44-7.55 (m, 3H, Ar-H), 7.65-7.77 (m, 2H, Ar-H). υ_{max}: 1820, 1730, 1630, 1595, 1580 cm^{-1}.

Attempt #4:

To a stirred solution of the acid (124) (55 mg, 0.226 mmol) in nitrobenzene (5 ml) under dry conditions was added oxalyl chloride (0.2 ml, 2.2 mmol, 10 equiv). The reaction mixture was stirred at room temperature for 3 h before it was placed under high vacuum for 30 min. A reflux condenser and drying tube were attached to the flask and the reaction mixture heated at 170°C for 18 h, after which time a large amount of black coloured, insoluble material had formed. The reaction was worked up by evaporation of the nitrobenzene solvent. No identifiable peaks were found in the ^{1}H NMR spectrum of the crude material.

Attempt #5:

To a stirred solution of the acid (124) (50 mg, 0.206 mmol) in dichlorobenzene (2 ml) under dry conditions was added oxalyl chloride (90 µl, 1.03 mmol, 5 equiv). The reaction mixture was stirred for 2.5 h before it was placed under high vacuum for 10 min to give a solution of the acid chloride (125) in dichlorobenzene.

This solution was heated under a condenser and drying tube at 170°C for 18 h before it was worked up by evaporation of the solvent under high vacuum. Resonances in the ^{1}H NMR spectrum of the crude material due to the starting acid (124) and the corresponding anhydride (132) were the only identifiable peaks.

Attempt #6: formation of *5-Benzoyl-1-keto-1,2-dihyro-3H-pyrrolo[1,2-a]pyrrole (106):*

To a stirred solution of the acid (124) (420 mg, 1.73 mmol) in dichlorobenzene (40 ml) under dry conditions was added oxalyl chloride (1.2 ml, 1.03 mmol, 5 equiv). The reaction mixture was stirred for 2.5 h before it was placed under high vacuum for 10 min to give a solution of the acid chloride (125) in dichlorobenzene.

Anhydrous zinc chloride (500 mg, 3.7 mmol, 2 equiv) was placed in one arm of a T piece of glassware. The second arm was attached to the reaction flask and the third to a high vacuum inlet. The zinc chloride was now made completely anhydrous by heating the arm of the T piece that contains zinc chloride, to *ca.* 200°C while under high vacuum. The system was released to nitrogen gas and the now completely anhydrous zinc chloride added to the reaction mixture. The system was capped with a drying tube and the mixture heated at 130°C for 18 h during which time dark coloured precipitate appeared. The reaction was worked up by addition of water, the mixture filtered through a celilte pad, and extracted twice with dichloromethane, the combined organic phases were washed once with water, dried, and the solvent removed under reduced pressure, dichlorobenzene was removed under high vacuum, to give the desired cyclized material (106) in a crude yield of 22% (86 mg, 0.38 mmol) which ^{1}H NMR spectroscopy indicated was the only pyrrolic product. Material which resonates in the aliphatic region was also present. ^{1}H NMR: δ 3.15 (t, J = 6.0 Hz, N-$CH_2C\underline{H}_2$), 4.76 (t, J = 6.0 Hz, N-$C\underline{H}_2CH_2$), 6.73 (d, J = 4.3 Hz, 1H), 7.00 (d, J = 4.3 Hz, 1H), 7.47-7.66 (m, 3H, Ar-H), 7.73-7.90 (m, 2H, Ar-H) (NMR data in agreement with lit.[79] values). ^{13}C NMR: δ 38.73, 44.31, 106.32, 124.19, 127.94, 128.27, 128.80, 128.88, 131.34, 132.27, 136.88, 137.86, 185.77, 191.23. υ_{max}: 1715, 1620, 1595, 1570, 1520 cm^{-1}. Mass spectrum: 225 ($M^{+\cdot}$), 197 (M - CO), 120 (M - PhCO), (M - C_7H_6NO).

2-Benzylpyrrole (133):

According to the procedure of Muchowski,[94] to a stirred solution of 2-benzoylpyrrole (4.77 g, 27.8 mmol) in *iso*-propanol (125 ml) was added sodium borohydride (0.74 g, 19.5 mmol, 0.7 equiv), and the reaction mixture refluxed for 18 h before it was shown to be complete by work-up (described below) of an aliquot of the reaction mixture and analysis by ^{1}H NMR spectroscopy which showed the absence of peaks due to starting material. The reaction was worked up by addition of water and removal of the *iso*-propanol under reduced pressure. The residual mixture was extracted twice with dichloromethane, and the combined organic phases were washed with water until *iso*-propanol had been completely removed, dried, and the solvent removed under reduced pressure to give the crude *title compound* as a red oil which ^{1}H NMR spectroscopy indicated was fully reduced and sufficiently clean for the next step. No yield was obtained at this point. ^{1}H NMR (200 MHz): δ 3.96 (s, 2H, CH_2), 5.98 (m, CH), 6.12 (m, CH), 6.62 (m, CH), 7.12-7.33 (m, 5H, Ph), 7.6 (br s, 1H, NH).

This reduction was not so readily accomplished in later attempts, and the test aliquot was returned to the reaction mixture, additional sodium borohydride (0.2 equiv) added and reflux continued. This test procedure was continued until the reaction was shown to be complete.

3-(2'-Benzylpyrrolyl)propanenitrile (134):

To a stirred solution of the crude 2-benzylpyrrole (3.92 g) from the first attempt in dioxane (15 ml) was added Triton B (0.2 ml) and acrylonitrile (1.81 ml, 27 mmol, 1.1 equiv) whereupon the mixture became warm. The reaction mixture was stirred in the dark for 18 h before it was worked up by removal of acrylonitrile and methanol under reduced pressure. Water was added and the residual mixture extracted with dichloromethane. The combined organic phases were washed three times with water, dried, and the solvent removed under reduced pressure to give a red oil which was distilled under high vacuum (135°C/0.05 T) to yield 2.85 g (13.5 mmol, 49% based on 2-benzoylpyrrole) of the *title compound* as a yellow oil which crystallized slowly. ^{1}H NMR: δ 2.20 (t, J = 7.2 Hz, 2H), 3.90 (t, J = 7.2 Hz, 2H,), 3.94 (s, 2H), 5.96 (m, 1H), 6.12 (m, 1H), 6.62 (dd, J = 1.7, 2.8 Hz), 7.14-7.32 (m, 5H, Ph). υ_{max}: 2970, 2250, 1610, 1500 cm^{-1}.

*5-Benzyl-1-keto-1,2-dihyro-3*H*-pyrrolo[1,2-*a*]pyrrole (135):*

Reaction was carried out as described for the corresponding benzoyl derivative (105) with use of 3-(2'-benzylpyrrolyl)propanenitrile (1 g, 4.76 mmol), dry ether (40 ml), boron trifluoride etherate (2.40 ml, 19.5 mmol, 4.1 equiv). Hydrogen chloride gas was bubbled through for 20 min before the flask was sealed and the mixture was stirred for 26 h, during which time red coloured precipitate formed. After removal of hyrogen chloride and ether, boron trifluoride etherate was evaporated under high vacuum. Sodium acetate (5 g) and water (80 ml) were added to the residue and the mixture heated at 80°C for 50 h to give a gummy residue which was extracted twice with dichloromethane, the combined organic extracts were washed once with water, dried, and the solvent removed under reduced pressure. The ^{1}H NMR spectrum of the crude material indicated a high level of purity: δ 3.00 (t, J = 6.3 Hz, 2H), 3.96 (t, J = 6.3 Hz, 2H), 4.00 (s, 2H), 6.31 (d, J = 3.9 Hz, 1H, pyr), 6.72 (d, J = 3.9 Hz, 1H, pyr), 7.16-7.34 (complex, 5H, Ar). The crude product was eluted through a short column of squat silica with dichloromethane, to give 0.466 g (47%) of the *title compound* as a pale yellow oil which crystallized slowly. ^{1}H NMR spectroscopy indicated greater purity than crude material. The column was washed with ethyl acetate to give a mixture of compounds, none of which could be identified by ^{1}H NMR spectroscopy.

Attempted oxidation of *5-Benzyl-1-keto-1,2-dihyro-3*H*-pyrrolo[1,2-*a*]pyrrole (135):*

Attempt #1:

To vigorously stirred bi-phasic mixture of the benzylic pyrrole (135) (14 mg, 0.066 mmol) in dichloromethane (2 ml) and water (2 ml) was added sodium metaperiodate (61 mg, 0.28 mmol, 4.3 equiv). The mixture was stirred for 18 h after which time no change from starting material was observable by TLC.

Attempt #2: preparation of *6-Bromo-5-benzyl-1-keto-1,2-dihyro-3*H*-pyrrolo[1,2-*a*]pyrrole (136):*

To a stirred solution of the benzylic pyrrole (135) (104 mg, 0.493 mmol) in carbon tetrachloride (10 ml) was added *N*-bromosuccinimide (88 mg, 0.493 mmol, 1 equiv) and a

catalytic amount of azoisobutyronitrile. The reaction mixture was refluxed for 45 min before it was cooled and filtered through a cotton wool plug. The filtered solution was allowed to stand for 2 d after which time it was refiltered and the solvent evaporated to yield 134 mg (0.462 mmol, 94%) of a mixture of predominantly the *title compound* and its 7-bromo isomer which was purified by flash chromatography. The compound could not be purified by recrystallization as it decomposed under heat. ^{1}H NMR: δ 2.89 (t, J = 5.9 Hz, 2H, H2), 3.93 (t, J = 5.9 Hz, 2H, H3), 4.04 (s, 2H, PhC$\underline{H}_2$), 6.77 (s, 1H, H7), 7.15-7.33 (complex, 5H, Ph)

Attempt #4: preparation of *5-Benzoyl-1-keto-1,2-dihyro-3*H*-pyrrolo[1,2-a]pyrrole (106):*

Following the procedure for DDQ oxidation by Rao[98]. To a stirred solution of the benzyl pyrrole (135) (20 mg, 0.095 mmol) in dioxane (8 ml) was added DDQ (65 mg, 0.284 mmol, 3 equiv). The reaction mixture was refluxed for 18 h before it was cooled to room temperature, filtered through a cotton wool plug and the solvent removed under high vacuum. The ^{1}H NMR spectrum indicated the reaction had gone to completion and the *title compound* was the only pyrrolic product. The sample was not purified further.

2-Benzylpyrrole (133) and *3-Benzylpyrrole (140):*

Prepared according to the procedure of Vander Werf.[99] To a stirred and cooled mixture of magnesium (4.33 g, 0.174 mol) and iodine (50 mg) in ether (100ml) was added ethyl bromide (15.5 ml, 0.208 mol) dropwise such that no reflux takes place. The reaction mixture was allowed to stir for 1 h at room temperature before a solution of pyrrole (11.86 ml, 0.184 mol) in ether (10 ml) was added dropwise and the resultant mixture allowed to stir for 1 h. The reaction mixture was now cooled to 0°C and kept at this temperature during the dropwise addition of a solution of benzyl bromide (9.60 ml, 0.127 mol) in ether (10 ml). The reaction mixture was allowed to stir at 0°C for 18 h, whereupon it was worked up by addition of an aqueous solution of ammonium chloride and ether was removed under reduced pressure. Emulsions formed when dichloromethane was used to extract the resultant aqueous mixture, these were broken by filtration of through a pad of celite. Two dichloromethane extractions

were combined, washed once with bicarbonate solution, water, dried and the solvent removed under reduced pressure to give the crude reaction mixture (16.1 g). This was distilled under high vacuum to remove pyrrole and give the *title mixture* (bp 130°C/0.04 T) in 32% yield (6.4 g, 0.041 mol) in an approximate ratio of 2/1. ^{1}H NMR of (140): δ 3.84 (s, 2H, CH_2), 6.07 (m, CH), 6.50 (m, CH), 6.69 (m, CH), 7.12-7.33 (m, 5H, Ph), 7.9 (br s, 1H, NH). The α isomer (133) has been described previously (p148).

3-(2'-Benzylpyrrolyl)propanenitrile (134) and *3-(3'-Benzylpyrrolyl)propanenitrile (141):*

According to conditions described for the single isomer (134) (p149), the following quantities were used, mixture (133), (140) from above (3 g, 0.019 mol), Triton B (0.2 ml), acrylonitrile (1.51 ml, 0.023 mol), dioxane (10 ml). The reaction mixture was stirred for 18 h before additional acrylonitrile (0.5 ml, 7 mmol) was added as TLC analysis indicated that the reaction was incomplete and the reaction mixture allowed to stir 42 h. The *title mixture* was obtained quantitatively. ^{1}H NMR of β isomer (141): δ 2.60 (t, J = 6.8 Hz, 2H), 3.99 (t, J = 6.8 Hz, 2H,), 3.77 (s, 2H), 5.99 (m, 1H), 6.38 (m, 1H), 6.57 (m, 1H), 7.14-7.32 (m, 5H, Ph).

*5-Benzyl-1-keto-1,2-dihyro-3*H*-pyrrolo[1,2-*a*]pyrrole (135)* and *6-Benzyl-1-keto-1,2-dihyro-3*H*-pyrrolo[1,2-*a*]pyrrole (142):*

Reaction carried out according to conditions described for the single isomer (135) (p150) with use of the following quantitites: mixture of isomers (134), (141) (11.53 g, 0.055 mol), boron trifluoride etherate (27.7 ml, 0.225 mol, 4.1 equiv) in dry ether (150 ml). The reaction mixture was allowed to stir for 18 h before it was worked up to give the crude *title mixture* in 88% yield (10.26 g, 0.0486 mol) which ^{1}H NMR spectroscopy indicated was of high purity. ^{1}H NMR of the β isomer (142): δ 3.11 (t, J = 6.1 Hz, 2H), 4.07 (s, 2H), 4.23 (t, J = 6.1 Hz, 2H), 6.26 (d, J = 2.2 Hz, 1H, pyr), 6.92 (d, J = 2.2 Hz, 1H, pyr), 7.16-7.34 (complex, 5H, Ar).

Attempted formation of *5-Benzoyl-1-keto-1,2-dihyro-3*H-*pyrrolo[1,2-a]pyrrole (106):*

Oxidation of the mixture of isomers (135) and (142):

Attempt #1:

According to the conditions of Harvey,[100] to a solution of the mixture of isomers (135), (142) (174 mg, 0.825 mmol) in acetic acid (80 ml) and water (16 ml) was added DDQ (560 mg, 2.47 mmol, 3 equiv) and the mixture refluxed for 18 hr before a portion was worked up by removal of solvent under reduced pressure. The residue was extracted with ethyl acetate/hexane, the extractions were filtered through celite and the solvent removed under reduced pressure. The residue was analysed by ^{1}H NMR spectroscopy which indicated only starting material.

Attempt #2:

Dioxane was purified by fractional distillation from lithium aluminium hydride. The fraction boiling at 99.5-100°C was collected and 2% water was added. According to modified conditions of Rao,[98] to a solution of the mixture of isomers (135), (142) (240 mg, 1.13 mmol) in purified dioxane 2% water (10 ml), was addded DDQ (775 mg, 3.41 mmol, 3 equiv), and the mixture refluxed for 42 hr. Work-up was by dilution of the reaction mixure with dichloromethane, this mixture was washed twice with 10% sodium hydroxide solution and once with water, dried, and the solvent removed under reduced pressure to give 71 mg (*ca.* 25%) of a mixture of the diketone (106) and starting material (135), as seen by ^{1}H NMR spectroscopic analysis. Further extractions of the basic aqueous phase with ethyl acetate yielded a further 20 mg of material

Methyl (E)*-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1'-yliden Acetate* and *Methyl* (Z)*-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1'-yliden Acetate (144*E*) and (144*Z*):*

To a dry flask containing activated zinc dust (450 mg, 6.9 mmol) was added a solution of the ketone (113) (100 mg, 0.83 mmol) and methyl bromoacetate (300 µl, 3.2 mmol, 4 equiv) in dry benzene (20 ml) via a dropping funnel. There was no obvious sign that the reaction had initiated. The reaction mixture was refluxed and stirred for 18 h after which time fresh zinc dust (300 mg, 4.6 mmol) was added and reflux continued for 4 h. The reaction was worked up by addition of ammonium chloride solution, and the resultant mixture stirred for 1 h before it was extracted with dichloromethane, the combined organic phases washed once with water, dried and the solvent evaporated under reduced pressure to give the *title mixture,* with a small amount of starting ketone (113) remaining, in 84% yield (133 mg, 0.70 mmol). Chromatography on silica (5% triethylamine/20% dichloromethane/hexane) gave the clean mixture of isomers. ^{1}H NMR (144*E*): δ 3.66 (dt, *J* = 2.3, 6.2 Hz, 2H), 3.72 (s, 3H, OMe), 4.13 (t, *J* =6.2 Hz, 2H), 5.99 (t, *J* = 2.3 Hz, 1H, =CH), 6.40 (m, 2H, Ar), 6.86 (m, 1H, Ar); (144*Z*): δ 3.31 (dt, *J* = 1.7, 6.8 Hz, 2H), 3.74 (s, 3H, OMe), 4.08 (t, *J* = 6.2 Hz, 2H), 5.54 (t, *J* = 1.7 Hz, 1H, =CH), 6.42 (m, 2H, Ar), 7.28 (dd, *J* = 1.1, 3.8 Hz, 1H, Ar).

Ehyl (E)*-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1'-yliden Acetate* and *Ehyl* (Z)*-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1'-yliden Acetate (150*E*) and (150*Z*):*

Following a general procedure of Rathke,[103] lithium diisopropylamide (3.33 ml, 5 mmol, 1.5 M solution in cyclohexane) was added to THF (20 ml). The solution was taken to -78°C, whereupon ethyl acetate (550 µl, 6 mmol) was added and the reaction mixture allowed to stir for 15 min. The ketone (113) (60 mg, 0.50 mmol) was added as a solid and the resultant mixture was stirred for 20 min before it was worked up by addition of ammonium chloride solution. THF was removed under reduced pressure and the resultant aqueous mixture extracted with dichloromethane. The combined organic phases were washed once with water, dried, and the solvent removed under reduced pressure to give a single pyrrolic product as seen be ^{1}H NMR spectroscopy which is presumed to be the expected enantiomeric mixture of

intermediate alcohols (149r). The mixture was dissolved in benzene (10 ml), a solution of ammonium chloride (10 ml) and zinc chloride (0.5 g) were added and the resultant biphasic mixture stirred vigorously for 2 d. Dichloromethane was added and the resultant mixture washed with water, dried and the solvent removed under reduced pressure to give the *title mixture* with alcohol (149r) still present, as seen by ^{1}H NMR spectroscopy of the crude mixture. Several of the compounds signals overlapped. Those signals that are distinct and correspond to the literature[106] are δ 3.32 (dt, *J* = 1.6, 7.1 Hz, 2H, H2 [minor isomer]), 3.68 (dt, *J* = 2.3, 6.6 Hz, 2H, H2 [major isomer]), 4.13 (t, *J* = 5.9 Hz, 2H, H3), 5.55 (t, *J* = 1.6 Hz, =CH [minor isomer]), 5.99 (t, *J* = 2.3 Hz, =CH [major isomer]), 6.39 (complex, 2H, pyr), 6.87 (dd, 1H, pyr).

Attempted formation of *1-Methylene-1,2-dihydro-3*H-*pyrrolo[1,2-a]pyrrole (151):*

Attempt #1: formation of Z-*1-Keto-2-(1',2'-dihydro-3'*H-*pyrrolo[1,2-a]pyrrole-1'-yliden)-1,2-dihydro-3*H-*pyrrolo[1,2-a]pyrrole-2-ylidene (154):*

According to a modified procedure of Peterson,[107] to a solution of TMS (4 ml, 29 mmol, 15 equiv) in ether (20 ml) at -10°C was added a solution of *sec*-butyllithium in cyclohexane (2 ml, 2 mmol, 1 equiv) over 15 min. The solution was stirred for 0.75 h before the ketone (113) (200 mg, 1.65 mmol) was added in ether (5 ml) and the reaction stirred at -10°C for 1 h then kept at 5°C for 18 h. The reaction was worked up by addition of sodium bicarbonate solution. The aqueous phase was extracted twice with ether, the combined organic phases washed with water, dried over sodium carbonate and the solvent removed under reduced pressure to give 130 mg of crude material. Chromatography (10% triethylamine/30% dichloromethane/hexane) gave the pure material. No yield was recorded. ^{1}H NMR: δ 3.88 (tt, *J* = 6.2, 1.7 Hz, 2H), 4,20 (t, *J* = 6.2 Hz, 2H), 4.88 (t, *J* = 1.7 Hz, 2H), 6.24 (dd, *J* = 1, 3.9 Hz, 1H), 6.46 (dd, *J* = 3.9, 3.9 Hz, 1H), 6.48 (dd, *J* = 1.9, 2.4 Hz, 1H), 6.71, (dd, *J* = 1, 3.9 Hz, 1H), 6.98 (dd, *J* = 2.4, 0.7 Hz, 1H), 7.01 (dd, *J* = 1.9, 0.7 Hz, 1H). ^{13}C NMR: δ 33.49, 45.25, 47.71, 105.83, 106.64, 115.57, 116.36, 120.21, 120.78, 120.97, 135.80, 136.90, 137.42, 180.88. υ_{max}: 1650, 1600, 1500 cm^{-1}. Mass spectrum: 224 ($M^{+\cdot}$), 130.

Attempt #2:

Potassium carbonate (700 mg, 5.1 mmol, 4.6 equiv), methyltriphenylphosphonium iodide (450 mg, 1.1 mmol, 1 equiv), and the ketone (113) (70 mg, 0.58 mmol) were ground finely separately and then mixed together. The mixture was placed in a bomb and heated at 150°C for 6 h. The reaction mixture was extracted with hexane to leave behind salts. The solvent was removed under reduced pressure to recover only starting material. No yield was recorded.

Attempt #3:

A solution of methyltriphenylphosphonium iodide (330 mg, 0.83 mmol), potassium carbonate (140 mg, 1.0 mmol), ketone (113) (100 mg, 0.83 mmol) and water (2 drops) in dioxane (3 ml) was refluxed for 6 h. The solution was decanted and the dioxane evaporated under reduced pressure. The residue was extracted with hexane, the resultant solution decanted and the solvent removed under reduced pressure to return the starting ketone (113) in 95% yield as seen by ^{1}H NMR.

Attempt #4: formation of *1-Methylene-1,2-dihydro-3*H*-pyrrolo[1,2-a]pyrrole (151):*

Prepared according to a general procedure of Wattansin.[114] To a solution of the ketone (113) (40 mg, 0.33 mmol, 1 equiv) in THF (3 ml) and toluene (5 ml) at 0°C and under anhydrous conditions was added a 0.5 M solution of the Tebbe reagent in toluene (1.32 ml, 0.66 mmol, 2 equiv) and the mixture was stirred for 0.5 h at this temperature. The reaction mixture was allowed to warm to room temperature and stirred another 2 h. Work-up was achieved by addition of methanol (1.5 ml) followed by dilution with ether (15 ml) and drying agent sodium carbonate. Solids were filtered off through a celite pad, and the filtrate concentrated under reduced pressure (100 mm Hg) at room temperature. The residual toluene solution was loaded onto a flash column of alumina and eluted with 3% dimethylamine/dichloromethane. The alkene (151) was in the first of two yellow bands which separated. No yield was measured. A trace of 2,6-di-*tert*-butyl-*p*-cresol and dimethylamine was present in the d-chloroform NMR solvent used. ^{1}H NMR: δ 3.21 (apparent tt, J = 6.7, 2.2 Hz, 2H, H2), 4.09 (t, J = 6.7 Hz,

2H, H3), 4.87 (t, J = 2.0 Hz, 1H), 5.24 (t, J = 2.4 Hz, 1H), 6.24 (dd, J = 0.8, 3.3 Hz, 1H, pyr), 6.36 (dd, J = 2.8, 3.3 Hz, 1H, pyr), 6.73 (apparent br d, J = 1.7 Hz, 1H, pyr). υ_{max}: 2900, 1620 cm^{-1}.

Reduction and re-oxidation of *Ketorolac (3r):*

To a stirred solution of ketorolac (3r) (100 mg, 0.39 mmol) in dry ether (15 ml) was added lithium aluminium hydride (119 mg, 3.1 mmol) and the resultant mixture allowed to stir 1.25 h. The reaction was worked up by addition of a saturated solution of sodium sulphate[116] and the coagulated aluminium salts extracted with dichloromethane, the combined extractions were dried and the solvent removed under reduced pressure to give the reduction product (161) in *ca.* 85% yield (81 mg). Compound (161) was unstable on silica and used directly in the next step without further purification. ^{1}H NMR spectrum remained uninterpreted.

Re-oxidation attempt #1:

According to the general procedure of Sharpless,[54] to a solution of compound (161) (81 mg) in the solvent system of carbon tetrachloride (1 ml), acetonitrile (1 ml) and water (1.5 ml) was added ruthenium trichloride (6.8 mg, 5% equiv) and sodium periodate (300 mg, 1.4 mmol). The mixture immediately turned a dark red colour which indicats polymerisation. TLC analysis after 1.25 h, confirmed that polymerisation occurred.

Re-oxidation attempt #2: formation of *5-Benzoyl-1-keto-1,2-dihyro-3*H*-pyrrolo[1,2-*a*]pyrrole (106):*

According to a general procedure of Ley,[115] to a mixture of anhydrous *N*-methylmorpholine-*N*-oxide (79 mg, 0.6 mmol) and powdered 4Å molecular sieves (600 mg) in acetonitrile (4 ml) was added a solution of compound (161) (24 mg) in acetonitrile (2 ml). The resultant mixture was stirred 15 min, whereupon *tetra*-n-propylammonium per-ruthenate (TPAP) (2 mg, 3% equiv) was added and the mixture allowed to stir under anhydrous conditions in the dark for 2.25 h. Dichloromethane was added and the resultant mixture washed once with sodium sulphite solution, once with copper(II) sulphate solution and the solvents removed under

reduced pressure. The residue was redissolved in dichloromethane, the solution washed once with water, dried, filtered through celite and the solvent removed under reduced pressure. ^{1}H NMR spectroscopic analysis indicated the diketone (106) as the major product amongst a mixture of pyrrolic compounds.

Re-oxidation attempt #3: formation of *5-Benzoyl-1-keto-1,2-dihyro-3*H-*pyrrolo[1,2-a]pyrrole (106):*

According to a general procedure of Carey.[117] To a solution of compound (161) (187 mg) in benzene (20 ml) was added activated MnO_2 (2.1 mg) and the resultant mixture was stirred for 1h. The reaction mixture was filtered and the solvent removed under reduced pressure to give a red oil in very poor yield (*ca.* 5 mg) which ^{1}H NMR spectroscopy indicated contained the diketone (106) as the only pyrrolic product and some unidentified aliphatic material.

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